Background Study

Commission of Inquiry on the Pharmaceutical Industry

Canada

MULTINATIONAL R&D ACTIVITY
IN THE PHARMACEUTICAL INDUSTRY

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February 1985

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Cat. No. RG48-1/3-1986E
ISBN 0-662-14494-5

CCAC No. 192 25176 E 86-05

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1. INTRODUCTION

1.1 Scope of the Study

The focus of this study is the location of private R&D activity in the pharmaceutical industry. Analytically, the issue is conveniently divided into two parts:

1) Determinants of location between the home country (headquarters) and all other countries (foreign subsidiaries);
2) determinants of location among the various host countries (foreign subsidiaries).

A similar, although not identical, way of approaching the problem is to examine centralizing versus decentralizing tendencies in location of R&D by pharmaceutical companies. Some aspects of the theory and empirical evidence on location of R&D within countries are then of relevance as well.

The discussion below draws upon the literature on foreign investment and multinational corporation as well as literature on R&D and pharmaceutical industry in general. Since only a small fraction of the large volume of literature in these different areas deals explicitly with the location of R&D activity in the pharmaceutical industry, inferences and extrapolations from other industries are made as appropriate.

1.2 Organization of the Study

Chapter 2 begins with a brief overview of the theoretical models of foreign investment activities by multinational corporations and explores their implications for the location of the activities of pharmaceutical multinationals. Particular attention is paid to the hierarchy of corporate functions and the similarities and differences in geographic dispersion of the R&D and manufacturing functions. The available empirical evidence on recent trends in international distribution of investment and R&D funds by U.S. - based multinationals if reviewed, with special attention to the development of Canada's share. Among the determinants of location of R&D activity identified in the literature, the main part of Chapter 2 concentrates on economies of scale in pharmaceutical R&D. Some evidence on relative international costs of R&D inputs is also surveyed and the relevant conclusions of several studies of intra-national determinants of location of pharmaceutical R&D are discussed.

In Chapter 3, the focus is on the level, structure and trends in R&D activity in the pharmaceutical industry. It begins with a selective review of the vast literature on government regulations of new drug introductions and their effects on the rate of innovation and private profitability of pharmaceutical R&D. The findings of these studies are qualified by reference to methodological problems with the existing measures of profitability. The chapter concludes with a discussion of the policy tradeoff between price competition in the industry and the rate of innovative activity. The specific issues reviewed in this context include patents, licensing, and the link between market structure and innovation.

In Chapter 4, Canada's ranking with respect to the most important determinants of location of industrial pharmaceutical R&D is evaluated in light on the available empirical evidence. The factors considered include size of the Canadian market, government policies in support of industrial R&D, and implications of "invisible imports of technology" via foreign-owned multinationals. The strength of the relevant scientific establishment in Canada in relation to that of other potential locations is assessed both qualitatively, by reference to expert opinions, and quantitatively, using statistics on scientific publications.

Chapter 5 concludes the study by summarizing briefly the main findings and making observations on the scope for possible policy action.

2. LOCATION OF OPERATIONS IN THE MULTINATIONAL PHARMACEUTICAL INDUSTRY

2.1 Introduction

The model of foreign investment expounded by Caves (1971, 1982) is a useful point of departure in the context of pharmaceutical industry, because the key factor giving rise to the existence of multinational corporation is its possession of "intangible" assets, the most important of which are knowledge and technology.

In this model, a firm produces in several countries for two reasons (see also Hirschey and Caves, 1981):

1) Imperfections in the markets for proprietary intangible assets (e.g. technology) make it advantageous to employ intra-firm allocation mechanism rather than arm's-length transactions. There are specific advantages to locating production in different countries, among them the possibility of minimizing the costs of inputs delivered at the production location and cost of outputs delivered to consumers. In addition, locating production facilities in a particular national market may induce a favourable shift in demand for the firm's product, since production facilities are usually complemented by the development of distribution facilities and adaptation of the product to local market conditions.

2.2 Relationship between the Location of R&D, Production and Marketing Activities

2.2.1 Hierarchy of Corporate Functions

The literature on strategic management (for a concise review, see e.g. Howells, 1983) identifies the corporate technology strategy as a "core" or "control" management function exercised at the level of corporate headquarters. This is contrasted with routine or "programmed" operations performed at the plant level. In the pharmaceutical industry, where the technological superiority of a firm is crucial for corporate growth, profitability and survival, the technological profile of the parent company is the key determinant of plant technology. By implication, branch plants in the pharmaceutical industry are "not dependent on their local environment for sources of technical information and services, or on their own unit-based resources, but rather are provided with resources and information via corporate contacts and linkages" (Howells, 1983, p. 153). Howells (1984) also suggests, however, that the evolution of many large industrial firms into multi-market divisional organizations sometimes changes the organizational position of R&D activity. Rather than being organized as a corporate-wide task, it may become necessary to have specialized research departments to serve the particular needs of different product divisions. This, clearly, has locational implications.

The location of R&D facilities is, in part, dependent on the location of production facilities. Two sets of factors are relevant for this dependence relationship: The advantage of vertical integration, and some special features of prescription drug markets.

Williamson´s theory of hierarchical structures sheds some light on the conditions under which the integration of production and research activities in one firm will be most advantageous. The point of departure is the notion that exchange of technological information can proceed either as a market transaction, or by means of vertical integration between the user and the supplier. A market transaction requires contractual relationship which may be costly, depending upon such circumstances as uncertainty, frequency with which transactions occur and the extent to which durable transaction-specific equipment is required.

Vertical integration becomes a preferred option as the complexity of the contractual arrangement increases. The advantages of vertical integration include encouragement of freer flow of proprietary information and reduced motivation on the part of the supplier to use information provided by the user to the competitive advantage of his rivals. The user confidence in the product claims is likely to increase because of continuous experimental use of the new technology by the tied user and reduced costs of information asymmetries. Disadvantages of vertical integration include the potential for discouraging the supplier´s search for information from independent users and the possibility that the tied user is forced to buy inferior products from the integrated supplier (see e.g. Globerman, 1980).

The second set of factors relates to the changing patterns of technology licensing in the modern pharmaceutical industry. Temin (1980, pp. 67-87) describes how the innovative drug companies around the Second World War gradually abandoned the practice of licensing their drug patents to others and began using them to retain a monopoly over production of their new drugs. Their reason for extracting rent in this fashion, rather than by licensing other producers, is that the required royalty would be very high (80% of sales revenue, assuming price elasticity of demand of 1.25) and thus difficult to enforce, subject to political pressures and public criticism. Moreover, exclusive production was then the established practice in other industries; it is more compatible with effective promotion by detailmen who can represent an exclusive producer better than several licensees. Exclusive production may also make it easier to practice price discrimination and to take advantage of the possibilities offered by the tax treatment of R&D expenditures.

2.2.2 Empirical Evidence

The interdependence between production and R&D activities does not, of course, necessarily require that they be located in the same geographic area. The empirical relationship, however, seems surprisingly strong. For example, a Conference Board survey of overseas R&D of U.S. multinationals during the period 1966-75 shows this to be the case especially in science-based industries. The distribution of U.S. direct investment by countries was closely correlated with the distribution by countries of U.S. overseas R&D (rank correlation coefficient of 0.92). The survey concludes that "there is strong evidence that overseas expenditures on R&D follow the investment dollar in science-based industries" (Creamer, 1976, p. 5).

Up-to-date information on Canada's share in the R&D expenditures of U.S.-based multinationals is not available. Canada's share of U.S. direct investment, however, has been steadily declining over the past two decades, as shown in Table 2.1. Given the close correlation between the location of R&D and production facilities, this trend is likely indicative of the pattern of R&D spending.

Table 2.1 U.S. Direct Investment Abroad in Manufacturing in Canada and All Countries, 1966-81

	U.S. Direct Investment Abroad		
Year	Canada (millions of dollars)	All Countries (millions of dollars)	Canada as percent of all countries
1966	6,697	20,740	32
1967	7,059	22,803	31
1968	7,535	25,160	30
1969	8,404	28,332	30
1970	8,971	31,049	29
1971	9,504	34,359	28
1972	10,491	38,325	27
1973	11,755	44,370	26
1974	13,450	51,172	26
1975	14,691	55,886	26
1976	15,965	61,161	26
1977	14,795	62,019	24
1978	15,736	69,669	23
1979	17,392	78,640	22
1980	18,877	89,161	21
1981	19,659	92,480	21

Source: U.S. Department of Commerce. Quoted from Mansfield (1984, p.30)

The share of R&D spending the U.S. multinationals (aggregate of all industries) placed abroad in 1980 was estimated at about 12% of their global total (Hirschey and Caves, 1981, p. 115). For the U.S. ethical drug industry, the ratio of foreign R&D to total R&D rose rapidly from 7.5% in 1965 to 16.9% in 1978 (Grabowski and Vernon, 1982, p. 333). This trend is attributed in part to the growing percentage of industry revenues derived from foreign markets and in part to less stringent regulatory controls governing early clinical trials abroad.

Mansfield, Teece and Romeo (1979) formulated the relationship between R&D and production activities more explicitly: Since overseas laboratories are frequently geared to the special needs of foreign markets, the percentage of R&D expenditures they spend overseas should be directly related to the percentage of their sales derived from abroad. The correlation should be stronger for sales from foreign subsidiaries than for sales from exports, because much of overseas R&D is done in support of foreign manufacturing operations. This hypothesis was confirmed by regression analysis based on a sample of 1970 and 1974 data for 20 U.S. firms belonging to 8 different industries.

While evidence indicates that the U.S.-based multinationals decentralized their R&D activities away from the U.S., Canada does not seem to have benefited. For all industries in the Conference Board survey, R&D in Canada by U.S.-based subsidiaries declined from 22% to 14% of the overseas total between 1966 and 1972. Similarly, R&D in the U.K. declined from 24.4% to 18.5%. The beneficiaries of this shift were Germany (increase from 22% to 31%) and countries such as Belgium, Netherlands, and Italy, whose combined total increased from 7.5% to 11.4% (Creamer, 1976, pp. 40-41). Again, in science-based industries the intercountry shifts in R&D activity were matched by shifts in direct investment.

In the pharmaceutical industry, the combination of a shift towards location of R&D facilities abroad and a declining prominence of Canada produced a rapid decline in Canada's share of the total R&D expenditures U.S.-based multinationals place abroad. A rough idea of the magnitude of this decline is provided in the last column of Table 2-2:

Table 2-2: Canada's Pharmaceutical Industry's Spending as a Percentage of Foreign R&D Spending by the U.S. Pharmaceutical Industry

Year	Canada's R&D expenditures (mill. Can.$) 1	Exchange rate 2	Canada's R&D expenditures (mill.U.S.$) col.1xcol.2 3	U.S. R&D expenditures abroad 4	Canada's Share of U.S. foreign expenditures (col.3:col.4) 5
1968	11	1.077	10.2	39.1	26.1 percent
1969	12	1.077	11.1	41.7	26.6
1970	13	1.044	12.4	47.2	26.3
1971	16	1.010	15.8	52.3	30.2
1972	17	0.991	17.1	66.1	25.9
1973	19	1.000	19.0	108.7	17.5
1974	21	0.978	21.5	132.5	16.2
1975	23	1.017	22.6	144.9	15.6
1976	26	0.986	26.4	164.9	16.0
1977	27	1.063	25.4	197.7	12.8
1978	31	1.141	27.2	222.0	12.2

Sources: Col.1: Statistics Canada, Science Statistics Service Bulletin 1978-83 and Industrial Research and Development Statistics 1982 (with 1984 forecasts)

Col.2: Bank of Canada, average of daily rates

Col.3: Grabowski and Vernon (1982, p. 333)

Note: Figures in col. 1 include Canadian-owned companies as well as subsidiaries of other than U.S.-based companies. Canada's share in Col. 5 is thus slightly overstated. The trend, however, should not be materially affected.

The Caves model predicts that the relationship between R&D activity of multinationals and their foreign operations works in both directions: The established multinational has the information needed to predict the return to innovation in various national markets, not just the home country. If the multinational's information network indeed represents an advantage for this purpose, it should be capable of achieving both a higher and more certain expected return from R&D than a similar single-nation company (Caves, 1982).

Mansfield, Romeo and Wagner (1979) attempted to estimate the effect of overseas sales opportunities on R&D. The large U.S. companies in their two samples expected to draw 29-34% of the returns from their R&D projects from overseas markets; this includes returns derived via foreign subsidiaries, through licensing, and through exports of innovative goods. The more research-intensive the company, the larger the share of its R&D returns that comes from outside the U.S. Thus, large firms based their R&D investments on the revenues they expect to earn worldwide rather than in any single country (Caves, 1982, pp. 196-197).

Contractor (1980), however, reports that over 90% of the U.S. firms he interviewed had motivated and amortized R&D expenditures only over the U.S. and "principal" overseas markets where their equity affiliates were located.

In contrast to R&D, pharmaceutical marketing is almost always a geographically localized function, since health care systems, disease patterns and product preferences vary among nations. This is an incentive for decentralization of marketing activities independently of the location of the company's production and R&D facilities (Burstall et al, 1981, p. 20).

2.3 Factors Influencing the Location of Production Activities

2.3.2 Characteristics of Pharmaceutical Production

Separate consideration must be given to location of the manufacture of final dosage form versus the manufacture of chemical ingredients. Conventional wisdom and available empirical evidence support the view (see e.g. Association of British Pharmaceutical Industry, 1984) that manufacture of final dosage form should ideally be located in close proximity to the market. Economies of scale available in the production of chemical ingredients, however, may make it imperative that the whole global operation be served from one or only a few locations. Moreover, pharmaceutical products are not bulky and transportation costs are low. Thus, competition among the host countries for location of both manufacture of chemical ingredients and R&D activity is inevitable. On the other hand, a large centralized plant is also less flexible and consequences of a breakdown are more serious (Burstall et al., 1981,p. 17). Hence some decentralization of production is rational.

2.3.2 International Distribution of Production Facilities

In general, the key determinants of centralization or decentralization are the existence of economies of scale in the production process, the size of the local markets and the attitudes of national governments, especially import restrictions and requirements for local production. The manufacture of active ingredients is normally much more centralized. Even large firms typically have only two or three such plants and rarely more than six. They are usually located in developed countries, especially in the multinational's home country or in countries with generous tax concessions. The main reasons for this locational pattern are: (1) perceived[1] significant economies of scale at this stage of production; (2) requirement of higher level of skills and training and developed infrastructure; (3) generally much less significant restrictions on imports of fine chemicals than on imports of finished pharmaceuticals (Burstall et al., 1981, pp. 68-69).

Decentralization of production facilities into several countries, even if uneconomical on the basis of economies of scale alone, is often necessitated by a variety of factors: Some countries make the license to market the product conditional upon the establishment of a production facility; sometimes doctors may be more willing to prescribe the product if locally manufactured; marketing staff view the existence of a local manufacturing facility as a promotional advantage (Burstall et al., 1981, p. 143).

Local formulation and packaging is a common practice in the industry: A typical medium size multinational with global sales of around $300 mill. in 1976 had 11 plants in 11 countries; a large multinational, with global sales of $950 mill. had 39 plants in 38 countries (Burstall et al., 1981, p. 68). The most common reason for local production were restrictions on imports of finished pharmaceuticals. Without this incentive, production would typically be found only in large markets. Other reasons included the convenience of satisfying local requirements for formulation and packaging and tax concessions offered by some smaller nations. These considerations override the existence of longer production runs at this stage: For example, Burstall et al., (1981, p. 44) report that in their U.K. interviews, "most pharmaceutical manufacturers agreed that costs are lowest when production is most fully centralized".

In worldwide distribution of the production of pharmaceuticals, the trend has been toward increasing dispersion: the proportion of world production accounted for by the largest 8 nations fell from 83% in 1965 to 78% in 1975 (Burstall et al., 1981, p. 30).

The degree to which different multinationals disperse their production abroad varies considerably. For example, the U.K. pharmaceutical companies sell over 50% of their putput in foreign markets. The four largest companies carry out about 30% of their production abroad. For the German pharmaceutical companies, foreign sales are over 60% of total sales. About 40% of their production and more than 50% of their employment are located abroad. Approximately 72% of the total output of the three dominant Swiss pharmaceutical multinationals was produced outside Switzerland (Burstall et al., 1981, p. 38 and pp. 118-120).

During the last two decades, international trade in pharmaceuticals rapidly increased. In all developed countries, imports represent a rising proportion of consumption and exports a rising proportion of production. This may reflect an increasing international specialization in production of pharmaceuticals.

2.4 Factors Influencing the Location of R&D Activities

2.4.1 An Overview

The results of numerous econometric studies, surveys and interview reports on this subject, covering a whole spectrum of industries and countries, have been succintly summarized by Caves (1982, pp. 198-200) as follows:

First, centralizing tendencies are strong and only about 12% of R&D by U.S. multinationals is located abroad. However, the share of R&D located abroad has been growing over the past two decades.

Second, overseas R&D is oriented more towards development and less towards basic research than is R&D in the home country (at least in the U.S.). However, basic R&D is also more footlose than applied research and some of it goes abroad to seek out particular scientific specialists.

Third, the larger the percentage of the global sales of the multinational enterprise which is accounted for by subsidiaries located abroad (i.e. the less the firm relies on exports to serve foreign markets), the higher the percentage of its total R&D which is performed abroad.

Fourth, the more important the economies of scale in research, the less it is decentralized overseas.

Fifth, the more a firm's overseas production is concentrated in a few subsidiaries (where R&D scale economies can be realized), the more of its R&D is performed abroad.

Sixth, multinational corporations also show some sensitivity to variations in the costs of R&D inputs from country to country. Decentralization increased during the 1960's when the U.S. research personnel were more expensive than their foreign counterparts, but stabilized when the cost differentials narrowed.

There is a consensus in much of the literature on R&D that product development for a local market is best carried out in the country for which it is intended. However, most pharmaceutical R&D is not tied to a specialized geographical market. The relevant locational factors then become the availability of economies of scale in R&D, relative costs in the various locations, supply and quality of R&D personnel (which depends on the quality of local scientific base, e.g. proven record of pharmaceutical discovery) and policy factors, including drug safety regulation and testing requirements. Other factors affecting decentralization of operations include the importance of pharmaceuticals within the company's product mix and locational factors affecting the nonpharmaceutical activities, management style of the firm influenced by organizational structure, management personalities, etc., and historical accident (see e.g. Burstall et al., 1981, pp. 20-22).

R&D may be conducted at the corporate headquarters (i.e. centralized) either to foster closer linkages with overall corporate policies or because of its orientation on basic or applied research which is not related to individual product lines. The main benefits of decentralized R&D derive from improved coupling with other organizational functions. Specifically, this refers to improved communication links with production and marketing, important especially in applied research and development work. A disadvantage may be the lack of specialized staff in the decentralized laboratories as well as higher unit costs of operating smaller research units. The lack of sufficient size also makes it more difficult to keep projects stable on a long-run basis and thus attract technical talent.

In the case of diversified pharmaceutical companies, it is generally recognized that drug research constitutes a distinct activity and, consequently, is carried out at the level of the pharmaceutical division. Within the division, however, centralization and decentralization take place along the lines of basic and applied research versus development work (Howells, 1984; Malecki, 1979).

Burstall et al. (1981, p. 71) identified three distinct models of geographical distribution of R&D activity observed within the major multinational pharmaceutical corporations:

1) One (or at most two) research centres in the home country carry out most of the important research and other establishments are confined to routine or applied research (the "sun and satellites" model).
2) Different types of research are located in different countries determined by their special characteristics (the "functional decentralization" model).
3) A firm may have several independent research centres, each carrying out most or all of the stages of the innovation process (the "let several flowers bloom" model).

As far as the available evidence indicates, no particular model can be associated with success of failure in R&D performance.

2.4.2 Economies of Scale in Pharmaceutical R&D

Published empirical findings on the economies of scale in pharmaceutical research show a wide range of results. Earlier studies, based on data for the 1950's, concluded that economies of scale in R&D were exhausted well below the largest observed firm size and diseconomies stepped in (Comanor, 1965; Grabowski, 1968; Monopolies Commission, 1972). More recently, data for a group of European and American companies during the 1960's showed constant returns to scale (Angilly, 1973). Schwartzman (1976) reported large economies of scale for a sample of U.S. companies.

Generally, studies working with the more recent data seem to show that: large firms spend more on research than small firms, produce more innovations of which a higher fraction are commercially successful and a disproportionately large number of them are rated as being of high therapeutic significance.

Following Comanor (1984, pp. 31-40), the various empirical studies can be usefully grouped into three categories, depending upon the problem they address and questions they ask: the relationship between R&D spending and firm size, the relationship between output of new drugs and size of firm or research establishment and the minimum efficient size of laboratory. They are briefly discussed in what follows.

A) Relationship between R&D spending and firm size

Earlier studies (Comanor, 1967; Mansfield, 1968) found that R&D spending in the pharmaceutical industry increases less than in proportion to the firm size. Grabowski (1968) fitted R&D expenditures during the period 1959-62 as a quadratic function of sales and also found a levelling off effect as the firm size grows large. Schwartzman (1976, p. 68), however, working with data for 1968-69, concluded that "as firm size increases, the relative research effort continues to increase"

While these studies established a relationship between R&D and firm size, it is not necessarily a causal one: Comanor (1984, pp. 32-33) cautions that both firm size and R&D spending are endogenous and statistical investigations should include such underlying determinants as output of the research process, cash flow and diversification of the firm's activities.

B) Relationship between research output and size of firm or size of the research establishment.

Comanor (1965) measured research output by the number of new products weighted by their sales during first two years after introduction. He found increasing returns to scale in R&D for small firm sizes (measured by pharmaceutical sales), but decreasing returns when size becomes moderately large. Vernon and Gusen (1974) attempted to answer the question whether large or small firms are more efficient in promoting technical change. They conclude that, holding R&D expenditures constant, larger firms have an advantage over smaller firms in the development of new chemical entities. They hypothesize that large firms are engaged in more activities and whatever knowledge they produce is more likely to be usable. Hence, there are increasing returns to locating fixed R&D staffs in larger firms.

Vernon and Gusen also estimated the relationship between average new product sales and firm size. They found a statistically significant positive coefficient, but it is not clear whether the superior performance of large firms is due to the greater therapeutic contribution of their new products or to their superior marketing.

Mansfield et al. (1971) report the finding that, relative to size, the most innovations were contributed not by the largest firms, but by the somewhat smaller ones. Schwartzman (1976), however, concluded that the largest firms discover relatively more drugs than small ones. Angilley (1973), on the basis of British data on new product introductions could not reject the hypothesis of constant returns to scale.

Surveying these contradictory findings, Comanor (1984, pp.39-40) conjectures that one reason for the discrepancies may be the different data periods: the earlier studies, finding diminishing returns to size, worked largely with the pre-1962 information. A second explanation may have to do with the definition of "new product". Mansfield et al. (1971) worked with "major distinct innovations" where small firms may be relatively more important. Schwartzman, on the other hand, included all new single entities. The contradictory findings are thus consistent with the hypothesis that large firms are more important with respect to the aggregate of all new drug introductions and smaller firms with respect to the most important innovations.

C) The minimum efficient size of a laboratory

Burstall et al. (1981, p. 43 and p. 71) summarize several OECD and U.K. studies, supplemented by their own interview estimates, pertinent to this issue. One finding is that there exists a threshold level of R&D spending below which a pharmaceutical company could only concentrate on minor improvements of existing drugs rather than on genuine innovations. A minimum viable unit should be large enough to work at least on three projects at the same time, spending about $10 mill. per year in the U.K. or $15-20 mill. in the U.S. (in 1977). A large company in the same year would work on 8-10 projects and spend $40-50 mill. in the U.K. or $60-80 mill. in the U.S.

The critical mass for a research establishment in the pharmaceutical industry is believed to be between 200 and 300 personnel. Below this level, research establishment is ineffective; above the threshold, significant economies in costs of services and overhead are realized. Diseconomies of scale are believed to set in when the research personnel reaches between 1,000 and 1,500 and management problems become intractable to the point where a second research centre becomes desirable.

Because of the presence of the threshold effect and economies of scale, only three of the 25 largest multinational companies in the world had an additional research establishment of approximately the same importance as the main research centre located in their home country. Only in one case was this establishment of greater importance than the one in the home country.

Mansfield, Teece and Romeo (1979) obtained estimates of the annual expenditures for an overseas laboratory of minimum economic scale from 27 U.S. multinational firms. For a laboratory doing research on a single product line the mean estimate of the minimum annual expenditures was $1 mill. The amount was higher for a laboratory dealing with several product lines and the ranges of estimates were large.

A survey by the PMA showed that a diminishing percentage of U.S. pharmaceutical firms operate research programs below the threshold level of $5 mill. While in 1968, 63% of PMA members had such programs, by 1973 this proportion dropped to 47%. On the other hand, programs over $20 mill. were operated by 11% of member firms in 1968, but by 21% in 1973. In large companies, the R&D expenditures per researcher with doctoral degree rose by 25% between 1968 and 1973; the corresponding increase for medium-sized companies was 20% (Burstall et al., 1981, p. 59).

In 1975, the average size for a sample of 25 U.S. laboratories was 271 professionals plus 289 technicians (Burstall et al., 1981, p. 70). In the six leading German pharmaceutical companies, the average number of researchers was 267 and an estimate of a threshold number for real success was 150 scientists. Six of the eleven companies in the sample analyzed by Burstall et al. (1981, p. 122) had less than this minimum. For a sample of nine French companies, the average number of R&D personnel was 380. Subsidiaries of foreign companies operating in France had research laboratories with only about one-third of this size (Burstall et al., 1981, p. 126).

2.4.3 Cost of R&D Inputs

Internationally comparable data on cost of doing R&D specific to the pharmaceutical industry are not available. Mansfield, Teece and Romeo (1979) developed an index based on information from 35 U.S. multinationals, belonging to 8 different industries, comparing the costs of R&D inputs in the U.S. with those at other locations. It shows that in 1965 the costs were about 30% lower in Europe (with considerable variations across countries, from low in the U.K. to high in Germany), 20% lower in Canada and 40% lower in Japan. However, the differential narrowed down by 1970 and almost disappeared by 1975:

Table 2.3 Mean Ratio of Cost of R&D Inputs to the U.S. Costs

	Location		
Year	Europe	Japan	Canada
1965	0.68	0.56	0.82
1970	0.74	0.60	0.86
1975	0.93	0.90	0.96

Source: Mansfield, Teece and Romeo (1979)

2.4.4 Empirical Evidence on International Distribution of R&D Activity

Research is considerably more centralized than production. Even the large pharmaceutical multinationals have no more than eight research centres and most have substantially fewer (Burstall et al., 1981, p. 69). Most companies have at least one research centre of considerable size, with a specialized library, computerized information centre, training establishment, research laboratories and a farm for animal and plant research. Centralization of research is viewed as conducive to synergies and thus economies of scale. Furthermore, a comprehensive R&D program requires the creation of multi-disciplinary teams and the complexity of management of such teams increases when research activities are decentralized.

The original function of an affiliate R&D facility is adaptive research (design of dosage forms, supply of analytical methods and standards, and analytical service to manufacturing facilities. A specialized affiliate R&D facility may be established because of the availability of local skills, interest of certain individuals or reputation of local medical schools or hospitals.

The functional progression from adaptive research to creation of new technology or a pharmaceutical product is predetermined by the scope of the research activity in the home country. However, the past profitability of the research conducted by the affiliate, demonstrated ability to undertake research and its self-financing capabilities are crucial.[2] Similarly, such policy measures of the host country governments as prices of pharmaceuticals negotiated so as to guarantee specified profit levels, the over-all ability of the affiliate to be self-supporting and the impact of the host country's policies on its profits also influence the degree of autonomy granted by the parent company.

Clinical research is most widely distributed internationally, often under contract to outside researchers. The location of this activity is determined by such factors as relative costs, usefulness for the drug registration procedure, the ease and speed with which the governments approve the test, previous performance of the testing institution, legal requirements in certain countries that tests be performed on their territory, etc.

Burstall et al (1981, p. 131) conclude that, in contrast to the traditional centralization of the research function, "an increasing number of the larger drug companies are managing two or more major research units - usually one in North America and one in Europe - and are increasingly taking advantage of the second-order capacities of different scientific communities." Thus, as mentioned above, some 17 percent of the global R&D spending by U.S.-based multinational pharmaceutical companies is now incurred abroad (Grabowski and Vernon, 1982, p. 333). The three dominant Swiss multinationals deploy about one-half of the total R&D personnel and R&D spending abroad, with a larger share of the development work being done by subsidiaries abroad.[3]

A survey of the location of research facilities for a sample of 12 large U.S., U.K., Swiss and German pharmaceutical multinationals in 1976 shows that by far the largest part of their research activity is performed in the home country and much of the rest is done in another large developed country, primarily the U.S., U.K. and Germany (Burstall et al., 1981, p. 70).

2.4.5 Location of Pharmaceutical R&D Within a Country

One of the theoretical models purporting to characterize this process is the "filter down hypothesis." It states that inventions and innovations are more likely to take place in large metropolitan areas of industrially mature regions. As the age of industries increases and their technology matures, their skill requirements are reduced and they are able (and forced by competitive pressures) to locate in areas with lower skills and lower wages. The reason is that as industries age, they become less dependent on external economies derived from information network and intensive contacts, available in the metropolitan areas. At the same time, it becomes more important to draw upon cheaper, less skilled labour found in less mature regions.

Howells (1983) tested the validity of this hypothesis with data from an interview survey (conducted in 1978) of a sample of 83 pharmaceutical manufacturing enterprises located in three regions of the U.K. For the case of production units within the U.K. pharmaceutical industry, Howells' empirical results do not support the predictions of the filter down theory: there appears to exist no statistically significant relationship between the various measures of technological sophistication of plants and the size of settlement in which they are located, the degree of urbanization or the broader centre-periphery regional setting. The conclusion is that while "high-order control and administrative functions of large multisite pharmaceutical companies have remained concentrated within the more central areas of Britain, their production units have been attracted to more peripheral or less urbanized areas." Some factors responsible for attractiveness of such peripheral areas include government regional policies, residential preferences for less urbanized areas, rising land/labour ratios, changes in labour skill requirements, and fewer problems with treatment and disposal of effluents generated by bulk processing of pharmaceutical chemicals.

Over 80 percent of the sample enterprises undertook some form of R&D activity, just over 40 percent were single-site enterprises and the remainder were multi-site operations. Companies with separate research departments or divisions were asked to indicate the "main factor" as well as "any other factors" which influenced the location of their R&D establishments. The most frequently mentioned "main factor" (34 percent of responses) was proximity to the company's pharmaceutical headquarters, the next factor was proximity to the main pharmaceutical production unit, attractiveness of the location for research staff (residential characteristics, schooling facilities, cultural amenities) and the availability of suitable premises and site.

Somewhat surprisingly, much smaller numbers of respondents cited such "main factors" as proximity to other research establishments, including universities, and proximity to sales/marketing department (only one company, or 2.6 percent of responses in each case considered these factors as "most important"). As for the "other factors" which generally influence location, proximity to headquarters, to production units and availability of suitable premises and site were among the most important. However, proximity to other research establishments (especially to major teaching hospitals) was rather prominent as well, particularly in connection with clinical trials of new drugs. Some small and medium-size companies reported reliance upon specialist independent laboratories for product testing.

Thus, the two most important factors determining the location of R&D were "internal" characteristics of the firm, i.e. proximity to the head office and to the main production unit. Proximity to the sales/marketing department, while mentioned as an important secondary factor by 18 percent of the respondents, was, surprisingly, given as the "most important" factor by only 2.6 percent of respondents. Howells (1984, p. 26) thus concludes that the dispersal of industrial R&D is closely related to fulfilling internal locational criteria and "may simply be a subsequent by-product of a decision to decentralize a head office of manufacturing unit."

Malecki (1979) analyzed the location of R&D facilities for a sample of 330 of the largest U.S. corporations for which corporate-funded R&D in 1977 was known and which had R&D facilities listed in the 1965 and 1977 Directories of Industrial Research Laboratories in the U.S. He found a trend toward a greater distribution of R&D laboratories, i.e. they are located in a greater number of metropolitan and non-metropolitan areas. Among the ten industry groups covered by Malecki's sample, drug firms showed the largest increase in the number of R&D laboratories per firm between 1965 and 1977 and had the fourth largest number of laboratories per firm in 1977. In other words, while decentralization of R&D activity took place in all ten industries, it was most pronounced in the drug industry.

3. TRENDS IN R&D ACTIVITY IN THE MULTINATIONAL PHARMACEUTICAL INDUSTRY AND THEIR DETERMINANTS

3.1 Introduction

The global R&D outlays are estimated at about $2 bill., i.e. 9% of global sales (Egan et al., 1982, p. 4). In the terminology of the standard OECD definitions of R&D, the bulk of pharmaceutical research must be described as applied R&D, with clinical and toxicological testing representing a substantial and increasing portion of the latter category. Basic research represents only 9.5% of the whole (Burstall et al., 1981, p. 39).[4]

An examination of the patterns of R&D spending and the number of new pharmaceutical entities introduced in a cross-section of nations reveals considerable productivity differentials. The traditional view, based on data for the 1960's and 1970's describes countries such as the U.K. and Belgium as exceptionally successful relative to their R&D spending. (Relative to manpower, the performance of the U.K. and U.S. is roughly similar, indicating that the superior per-dollar productivity is due to lower labour costs in the U.K.). France and Italy are less successful than would correspond to their research effort. Japan was viewed as unsuccessful in product innovation in relation to the R&D inputs (Burstall et al., 1981, p. 43). Current assessment of the R&D performance of the 1,700 Japanese drug companies by U.S. industry executives is, however, very different. They are quoted as being "impressed with the quality of their research...for a nation that has just started to do pharmaceutical research, they've come out with some elegant and successful products." They expect that Japanese penetration of the U.S. and other foreign markets will be "evolutionary" because the U.S. companies are at present significantly ahead (New York Times, February 24, 1985).

3.2 The Level and Structure of R&D Activity

3.2.1 Sources of New Drugs

A substantial segment of the traditional economic literature on the drug industry has argued that the industry leaves basic research to governmental and university institutions and builds its own research and product development upon the discoveries of the non-profit sector. In addition, it has been argued (see e.g. Comanor, 1966) that the U.S. industry has not concentrated on major innovations, but rather on drugs that have frequent use and "doctors' confidence." The corollary of this argument then is that compulsory licensing, while it might reduce the total R&D expenditures, need not reduce the introduction of the "most important new products."

More recently, a number of studies have concluded that a large majority of new drugs have been developed by industry laboratories and that the industry share has been increasing. For example, Schnee (1973) found that during the period 1935-49 some 52% of drug discoveries came from the industry. During 1950-62, the industry share rose to 69% and during 1963-70 to 82%. Paul de Haen's tabulation of new single-entity compounds introduced in the U.S. in 1978 shows that 20 were discovered by companies, while the remaining 3, including one from France, came from academic institutions (Egan et al., 1982, p. 76).

Schwartzman (1976, pp. 73-81), after a review of various U.S. studies concurs with the view that the industry's share has been large and growing. When the new drug products are weighted by sales, the importance of industry sources of innovation is even greater. The problem of the choice of weight (therapeutical/contribution vs. commercial value of the new product) illustrates a fundamental difficulty in assessing such statistics - a problem well known since the Kefauver hearings and described by Comanor as "battle of the lists" (i.e. the debate as to the ranking of the important drug discoveries).

A British study by Reekie, based on an analysis of U.K. patent statistics since 1900 represents an extreme in this debate: it concluded that at least 95% of patents originated in the industry. This is consistent with the observation that only two major drug discoveries during the past thirty years originated outside the pharmaceutical industry - oral contraceptives and the cephalosphorin antibiotics (Burstall et al., 1981, pp. 91-92).

The comparability of research output between industry and nonindustry sources is, of course, open to question, since the two sets of institutions have different goals. Universities and hospitals lag as a source of pharmaceutical innovation behind the industry mainly because they have many other functions. Furthermore, universities are oriented toward production of pure knowledge rather than utilization of knowledge and innovation. The industry, on the other hand, emphasizes modifications and translation of new discoveries into marketable products. The two sets of institutions can, therefore, be viewed as complementary, since they do not draw resources from each other.

The distribution of the research output within the industry sector has received substantial attention as well. Mansfield et al. (1971) concluded that, at least during the period 1950-65 and in the new therapeutical areas, the smaller companies were capable of effective innovation.

However, since the new therapeutic markets were generally small, the economic impact of such innovation was limited. The advantage of large companies was further enhanced whenever international sales were required to make a product commercially viable. This is the rationale for the propensity of small innovative companies to enter into licensing or joint venture agreements with large multinational companies to take advantage of their worldwide marketing and distribution facilities.

In more recent periods, characterized by rising costs of drug research, the small firms are less and less able to maintain R&D programs with significant impact on the industry. In the view of Burstall et al. (1981, p. 103), the contemporary pharmaceutical industry is characterized by a two-tier structure: Large international companies, in the upper tier, provide most of the new products in the "high technology" markets and firms in the lower tier operate in established, low-technology markets. Studies of the patterns of diffusion of pharmaceutical innovation show that the multinational companies tend to discover more significant drugs and their less significant discoveries get more widely diffused over the world markets. The large firms were also shown to introduce rival products earlier within newly emerging therapeutical markets. The tightening of regulatory procedures and associated increase in cost of doing research seems to have added to the advantages of the large firms. Empirical evidence on this matter is discussed below.

3.2.2 Impact of Regulation on Drug Discovery

The connection between the tightening of regulatory standards for new product introduction in the U.S. (in 1962) and the subsequent trends in pharmaceutical innovation has been the subject of an extensive discussion. Empirical studies by Baily (1972) and by Peltzman (1973) both concluded that the 1962 regulatory change had a negative effect on drug innovation. Subsequent econometric studies have shown, however, that the problem of separating the impact of regulation from other determinants of new product introduction has not yet been satisfactorily resolved. Recently Temin (1980, p. 5) observed that the 1962 Amendments to the Drug Act could not have caused the observed reduction in new product introduction, since "at almost the precise time these amendments were passed, the postwar rate of new drug introductions fell off sharply, from an average of 50 per year in the 1950's to an annual average of 20 in the 1960's".

The mechanism through which increased regulatory stringency affects R&D spending by the industry is twofold (Comanor, 1984, pp. 76-85). First, the required additional tests increase the cost of R&D and, second, the reduced expected profitability of R&D will cause a reduction in R&D expenditures. Wiggins (1984) found no effect of the 1962 tightening of U.S. regulatory standards for the period 1965-68, but a significant effect for the period 1971-76. The increased regulatory lag (measured by the average time from submission of a New Drug Application to approval) as compared to the lag observed in 1962, is estimated to have reduced research expenditures in the drug industry in the 1970's on average by 24% with considerable variation across therapeutical classes.

Grabowski and Vernon (1976, 1977) argue that the increased costs and risks due to tightening of regulatory standards induced concentration of innovation in large firms by increasing the economies of scale in pharmaceutical R&D. There is evidence that large firms account for an increasingly large proportion of new drug introductions. However, concentration of sales has not increased and new products account for a declining share of total sales. While the smaller number of new products means that each approved product is facing less competition from other new products, overall price level is more significantly affected by competition from non-patented or generic products.

A leading alternative explanation for the rapid decline of new product introductions in the post-1962 period is the "depletion of research opportunities" hypothesis. It states that an unusually large number of new products were introduced in the post-war period as a result of an explosion of underlying scientific knowledge. Once the stock of knowledge became depleted, the flow of new products slowed down.

Critics of this hypothesis argue that, quite to the contrary, new ideas proliferate at an increasing rate. An entirely new phenomenon relevant in this context is the development of medical sciences in the direction of establishing theories concerning chemical and therapeutic activity of drugs. This, combined with advanced in molecular biology, is expected to enhance the rate of drug innovation (see e.g. Helms, 1981, pp. 23-24). It is, nevertheless, possible that while knowledge has been expanding, "it is the transmission of this knowledge into usable therapies that is falling behind" (Wardell, quoted in Comanor, 1984, p. 74). Egan et al. (1982, p.

173-174) perceive a shift, rather than a depletion, of research opportunities. They believe that regulation caused resources to flow out of the drug industry into the economy in general. The government imposes taxes to encourage research in areas other than drugs (including other forms of therapy).

Wiggins (1981, reviewed in Comanor, 1984, pp. 72-76) evaluates the impact of the 1962 Amendments by examining the FDA approval times for new drugs separately for different therapeutical markets. After correcting for the volume of research spending, he finds that the new product introductions declined by 52%, on average, as compared to the level which would result if the regulatory delays remained at their pre-1962 levels. The decline varied from 34% in antiinfectives to 81% in cardiovasculars. Regulation, however, also had a depressing effect on the volume of research, primarily through an increase of research costs per new product. In a more recent study, Wiggins (1984) compares the degree of regulatory stringency (as measured by the average time from submission to approval for new drug applications) across therapeutical classes after 1962. He shows that, while the decline in new product introductions was the largest in the Central Nervous System's products, the regulatory delay for these products was slightly below average for all other products. Similarly, a large decline was observed in antiinfectives, yet the regulatory procedures in this therapeutic class were among the least stringent. Wiggins thus concludes that increased regulatory stringency did not account for the decline in new product introductions. He hypothesizes that the relevant factor may have been the depletion of research opportunities.

Apart from the effect on the rate of new product introductions, the tightening of regulatory standards in the U.S. has been held responsible for several other developments: First, shift of R&D activity from the U.S. to other countries. This is manifested by the U.S. firms conducting an increasing share of their R&D abroad. For this and other reasons, drug discoveries from foreign laboratories now account for about 40% of U.S. new product introductions (Grabowski, 1982, p. 84). Second, many new drugs are made available to consumers in other countries (e.g. the U.K.) long before they become available in the U.S. (the "drug lag"). Third, the declining rate of return in the drug industry.

After reviewing the voluminous empirical literature dealing with these issues, Grabowski and Vernon (1982, pp. 322-325) conclude that the problem of isolating the effects of regulation on innovation from other confounding effects (e.g. depletion of research opportunities) has not been satisfactorily resolved. The regulatory lag appears to be narrowing, in part as a result of "more realistic" regulatory standards in the U.S. and in part as a result of a trend to tightening of regulatory procedures abroad. Finally, the specific mechanisms through which the various regulatory and nonregulatory factors affect the levels of research input and research productivity "await a more extensive and disaggregative analysis."

3.3 Private Profitability of Drug Innovation

3.3.1 Approaches to Measuring the Rate of Return on Innovation

In order to explain why some firms spend more on R&D than others, or why some firms realize available economies of scale to a greater extent than others, it is necessary to examine the connection between R&D spending and actual and prospective returns on R&D.

In an early investigation, Baily (1972) assumed a proportional relationship between the number of new products and past R&D expenditures (i.e. constant returns to scale in R&D). In a multiple regression, with the ratio of the number of new drugs to past R&D expenditures as the dependent variable, a measure of depletion of research opportunities obtained a negative coefficient, lending some support to the depletion hypothesis. Major pharmaceutical firms were found to earn normal returns on older products, but high returns on newer ones (throughout the period of patent protection). An R&D function was estimated for the whole industry to calculate the marginal research cost of developing a representative new drug. Next, a returns function was estimated for six firms to obtain the prospective returns from introduction of a new drug. From the two sets of figures, Baily then calculated the internal rate of return on past investment in R&D which was shown to decline from 34% in 1954 to 25% in 1961.

Schwartzman (1976) first determined the average R&D costs per new chemical entity. Next, he estimated the average sales per new chemical entity in 1972 and multiplied it by the average gross profit margin for six major firms to obtain a measure of return on R&D. The expected rate of return on R&D performed in 1973 was estimated at 3.3% (Schwartzman considered this to be an upper limit of the rate of return). By comparison, the rate of return on R&D performed in 1960 was estimated at 11.4% (this number is considered to be the lower limit of the rate of return). Critics (Comanor, 1984, pp. 42-44) note that Schwartzman's procedure amounts to estimating marginal return by means of average profit margins which is a different concept, and includes earnings from both new and old products as well as from non-pharmaceutical items. In addition, he assumed a 50% tax rate while the effective tax rate on profits before taxes plus R&D was only 35.7%. Thus, his calculated rate of return understates the correct magnitude.

Grabowski and Vernon (1982) calculated the number of years needed to recover the cost of R&D investment. For the average of new chemical entities introduced between 1970 and 1976, assuming the discount rate of 10%, pharmaceutical firms would need 19 years to break even. When the discount rate of 8% is assumed, the period is reduced to 12 years. In addition to the discount rate, the results are also sensitive to the assumptions made about production costs and foreign sales. Accordingly, the calculated payoff periods can fall within a wide range, but they appear to be rather long in relation to a typical product life.

Even allowing for the measurement problems, arbitrariness of some of the assumptions and wide range of available estimates, the evidence of a declining trend in the rate of return on pharmaceutical R&D is rather convincing. Furthermore, "the reader is left with the conclusion that the average returns generated by new chemical entities may now be less than average development costs, but there is also a large number of new products which generate much higher returns" (Comanor, 1984, p. 48).

In spite of the low and declining rate of return on innovation, the R&D expenditures of U.S. pharmaceutical companies have been growing in real terms and their R&D-to-sales ratio remained roughly constant over the past two decades: it was 8.3% in 1965, reached the high of 8.8% in 1970 and the low of 8.2% in 1978 (Grabowski and Vernon, 1982, p. 333).

This apparent inconsistency between low (and declining) rates of return and growing expenditures on R&D can be rationalized by reference to several factors: First, the adjustment process contains long lags, inherent in the relative inflexibility of R&D activity. Wiggins (in Helms, ed., 1981, p. 83) also argues that - in the earlier periods at least - the tightening of regulatory standards did not apparently affect R&D spending since the decision-making structure of pharmaceutical companies could not adapt to incorporate this new factor. Second, the cash flow margins during the periods under study were still relatively high due to the large numbers of new product introduced during the 1950's which were still under patent protection in the 1960's and part of the 1970's. Third, for some new chemical entities, the rates of return are much higher than average, hence the incentive for innovation remains powerful. Fourth, some of the published calculations of the rate of return on innovation contain a downward bias. In addition to the observations made above, Woltman (in Helms, ed., 1981, pp. 49-52) notes that the present value of revenues employed in such calculations should properly be compared with uncapitalized development costs since the drug companies write off R&D expenditures fully in the year when they are made. On the other side of the argument, however, some portion of the sales revenues from new products should be treated as return to promotion activities developing the new market. Thus, the net return to R&D may be considerably reduced. Fifth, Woltman hypothesizes that pharmaceutical firms may consistently underestimate the risks of product failure, perhaps because they are risk takers. This may be a part of the explanation why they continue to spend on R&D in spite of declining returns to innovation.

3.3.2 Profitability of the Drug Industry

Historically, the reported accounting rates of return for the drug industry exceeded the average for all manufacturing, although the difference has narrowed down somewhat in recent years: The after-tax rate of return on stockholders equity in the U.S. pharmaceutical industry in 1956 was 17.6% compared with all manufacturing average of 12.3%; the two rates were 20.3% and 13.4% in 1966 and 19.3% and 16.4% in 1979. It should be noted, however, that rates of return in the pharmaceutical industry were much more stable than in all manufacturing: They reached a minimum of 16.7% in 1961 and maximum of 20.3% in 1965 and 1966. For all manufacturing, the minimum was 8.6% (in 1958) and maximum (in 1979) was 16.4% (based on Grabowski and Vernon, 1982, p. 297.) This relationship between pharmaceutical and manufacturing rates of return prevailed already before the War, i.e. before the development of the modern pharmaceutical industry (Temin, 1980).

Literature based on the Kefauver hearings highlighted the persistently higher-than-average accounting rates of return as an indication of resource misallocation. The more recent literature notes that accounting rates of return do not reflect the economic rates of return because of the practice of expensing rather than capitalizing R&D and promotional expenditures. However, even the adjusted rates of return do not necessarily reflect the *expected* rate of return and do not separate the returns on R&D from returns on other activities; they are thus not the concept relevant for R&D decisions (Virts and Weston, in Helms, ed., 1981, p. 23). Stauffer (1975) argues further that all R&D spending should be treated as an asset, not just the cost of successful R&D projects, since unsuccessful R&D is an unwelcome but integral part of the process of obtaining successes and must be charged against the future income streams generated by the fraction of the expenditures that are successful. He also points out that the lag between R&D expenditures and results entail opportunity costs, yet it is not recognized in conventional accounting. Profitability measured by the conventional accounting concepts is thus overstated.

The methodologies of accounting adjustments differ from author to author, but the adjusted profit rates are typically lower by a substantial margin. For example, Ayanian (in Helms, ed., 1975) reports a reduction from 17.7% to either 14.6% or 13.69% (depending upon assumptions about rate of depreciation) in 1973, solely as a result of adjustments. Similarly Clarkson (1977), also for 1973, reports a reduction from 17.76% to 10.64%.

Comanor (1984, p. 7) points out a fundamental difficulty of measuring price-cost margins and calculating the Lerner index of monopoly in an innovative industry: When technology is not stable and not characterized by constant returns to scale, production costs are not an adequate approximation of marginal costs. Furthermore, over a longer time horizon, the cost of R&D may be a part of marginal cost.

3.3.3 New Products, Pricing and Profitability

Schwartzman (1976), Bond and Lean (1977) and Statman (1981) have shown that the first seller in the market typically maintains its market position without substantial price declines. This is largely attributed to brand loyalty enjoyed by the original patent holder (Comanor, 1984, pp. 27-28). A large established producer has a further advantage, since a familiar brand name is better received by doctors and a large-scale marketing effort can only be sustained by a large firm.

In contrast with the traditional view, Teeling-Smith and Reekie, among others, have argued that high-priced drugs are successful only if they are superior to the competing products. Teeling-Smith (1975) characterizes the profit-maximizing approach to new product introductions as "price skimming." Initially, the price is set high, since in the short run the demand for innovative product is inelastic. As substitutes appear and as patents expire, price tends to fall toward marginal variable cost. Since the marginal variable cost of producing drugs is very low, additional consumer surplus must be captured in the post-introduction period to recover the fixed cost of R&D. A non-innovative drug, on the other hand, employs penetration pricing strategy.

Reekie (1978) tested these hypotheses with U.S. data for the period 1958-75. He found that new chemical entities representing an important therapeutic gain were, at the time of introduction, priced at a higher level, relative to competing products, than drugs with modest or no therapeutic advantage. As new competition becomes likely over time, prices decline. The estimated price elasticity of demand is lower for "important" drugs than for "modest" innovations (but, paradoxically, drugs with "no innovative content" were shown to be least elastic of all). The price elasticity of demand for individual new chemical entities is shown to increase over time. Reekie considers the above behaviour to be consistent with the competitive model, even though price discrimination is clearly present (Egan et al., 1982, pp. 48-49). Similarly Telser (1975), in an analysis of a cross-section of therapeutical markets, observed that high concentration ratios do not preclude high entry rates of new products. He thus concludes that there are no effective barriers protecting the market power of existing brands.

3.4 Policy Issues

3.4.1 Statement of the Problem

"The essential trade-off pertinent to this industry is the choice between competitive prices and quantities for existing drugs and extensive pharmaceutical innovation" (Comanor, 1984, p. 92). This, in turn, leads to the question of the appropriate rate of return from pharmaceutical innovation. The policy problem then becomes the comparison of social benefits from policies encouraging innovation with social benefits generated by increased competition from lower-priced products.

From another perspective, government policies can be seen to affect drug innovation both on the supply side and on the demand side. On the supply side, they include not only policies relevant to Comanor's "tradeoff", but also regulation of new drug introductions which affects the cost of drug development and testing as reflected in the trends in costs per new chemical entity produced. On the demand side, the expected revenue from drug innovation is affected by import policies, formularies, maximum allowable cost programs, product substitution laws, etc. Their impact is reflected in data on sales and marketing forecasts of future sales of pharmaceutical products.

3.4.2 Patent Protection

Patent policies and compulsory licensing affect both the supply side and demand side of drug innovation and have received considerable attention. On the one hand, it is argued that patents and the returns they make possible are a necessary incentive for R&D. On the other hand, it has been asserted that drug research is largely imitative and meaningless, and patents enable false product differentiation to occur and so to create monopolies within therapeutic submarkets.

For example, Schifrin (1967) argued that shortening of patent life to 3 years would eliminate "unnecessarily high" profits without undermining incentives for R&D, since the industry is characterized by high turnover of products and obsolescence. The greatest portion of sales occurs in the first few years after introduction and most firms conservatively estimate the life of a product at 7 years to recoup outlays.

Comanor (1964) supports the patent system on the grounds that it strengthens and encourages chemical product differentiation which is the primary form of technical change in the drug industry. Comanor also concludes that the drug industry has a greater incentive for product than for process innovation because "where producer rivalry is high and the effective life of individual products is short, firms are unwilling to invest large amounts toward reducing production costs...by the time new techniques are developed...demand for the product may have dropped to a relatively low level."

It is often observed that industry and non-industry pharmaceutical research complement each other, the development of new areas of therapy being primarily the function of non-industry research. If this is the case, then a weakening of patent protection, while causing some reduction in the level of industry research, would not lead to a loss of new forms of therapy. Comanor (1984, p. 64) conjectures that the "prospective effect on pharmaceutical prices could foster sufficient benefits to overcome this loss."

Steele (1964) believes that approximately constant returns apply to production and thus large drug firms have no competitive advantage, except in large-scale advertising and distribution. Monopolization occurs through the use of patents and brand names to create a false differentiation of the product. Patents favour large firms, since a "patent is merely an invitation to costly litigation, and the only advantage a small firm can take of a patent is to sell it to a rival." He also contends that R&D is not an important argument for maintaining patents, since most drug industry research amounts to molecular manipulation.

Egan et al. (1982, pp. 60-62) levy a number of criticisms against Steele's analysis; they refute the charge of spurious product differentiation on the grounds that each claim for a prescription drug product must be demonstrated to the satisfaction of FDA and thus product differentiation is more likely to be authentic. (Steele, of course, wrote in 1964, barely after the introduction of the "efficacy" requirement. Similarly his discussion of the profitability of the industry does not take account of the subsequent findings of biases in accounting profit rates which result from non-capitalization of R&D expenditures).

The demand-side aspect of patent protection, compulsory licensing and related policies have received attention in Canada (e.g. Gorecki, 1981), but much less in the U.S. In the assessment of Egan et al. (1982, p. 54), "the scholarly literature thus far has not addressed the issue of the economic impact on the funding of R&D by the research-based companies should the FTC and other agencies succeed in making product selection by pharmacists virtually universal." And "the issue is important...because government efforts that mandate that price must be the all but exclusive criterion for selection among multisource drugs can significantly affect expected returns from R&D and therefore industry's willingness to engage in R&D."

Grabowski (1982) views as inadequate even the recent U.S. Patent Term Restoration Act, designed to strengthen patent protection of drug products. The reason is that patent restoration cannot fully compensate for the regulatory delay because it affects only the latter years of product life, while many products will face competition before patent restoration takes effect. Because of time value of money, any change affecting the front end of product life is much more significant. For example, Grabowski and Vernon (1982) found that shortening of the new product approval process by 1.5 years would reduce the time it takes a drug company to recoup its R&D investment from 19 years to 14 years.

3.4.3. Patent Licensing

There seems to be a consensus in the literature that the pharmaceutical industry differs from many others in that licensing for cash considerations is infrequent. However, considerable cross-licensing exists, sometimes with cash transfers to compensate for differences in values of the patents being exchanged. In valuing drugs for cross-licensing, the incurred R&D costs are often considered as "an important benchmark of value" (Contractor, 1981, p. 177). Telesio (1979, p. 23) quotes industry executives to the effect that "to develop a specific drug, they may need licenses for one or more intermediates from other patent holders". Other sources attribute the frequency of cross-licensing in the industry simply to "high costs of R&D".

Meaningful inter-industry comparisons of royalty rates can be made only if the agreement does not include cross-licensing and if the parties are independent (unaffiliated) firms. A number of such comparisons are quoted in the literature; almost invariably, the royalty rates arrived at in an unregulated market transaction are higher in pharmaceuticals than in other industries.

For example, Telesio (1979, p. 41) quotes a European chemical company which claimed royalties for pharmaceuticals in the range of 5-10% of licensee sales revenues while for dyes it was around 4% and for plastics about 3%. Another European chemical company charged royalties on its pharmaceutical products as high as 12% of sales and a U.S. pharmaceutical company gave an average royalty rate of 5% of sales. Other reported royalty rates: European non-electrical industry manufacturer (2-3%); European machinery company (2-5%); a U.S. food processor (3%); high-volume items generally (3-5%); low-volume items generally (10%); average of all royalty rates for a variety of industries (5%); agreements between U.S. and German firms in a variety of industries (2-10%); world semiconductor industry (4-6%).

Contractor (1981, p. 50) concludes that the royalty bargaining is influenced by "industry norms": 10-15% for pharmaceuticals, 3-5% for data processing, 2-3% for chemicals, 2% for consumer industries, 1% or lower for petroleum industries, 4-6% for wood and paper, less than 0.25 to 5% for the automobile industry. However, he cautions that individual contracts widely deviate from industry averages. Moreover, the above "norms are based more on executive impressions and sketchy surveys that have appeared in U.S. licensing-executive journals than on hard evidence. There is no indication of the extent of their use in the U.S. and no data for overseas, where licensees may even be ignorant of their presumed existence".

A recent survey (Rostoker, 1983-84) of licensing practices of 37 U.S. corporations over the five-year period ending in 1980 yielded results consistent with the above observations: The pharmaceutical industry, together with the associated chemical industry, provided the highest royalty rates to patent licenses, ranging up to 15 percent of sales (the other industries represented in the sample were electrical, mechanical, petroleum and transportation).

In-depth interviews with licensing executives of 12 U.S. firms (Contractor, 1981, p. 79) indicate that R&D expenditures in most industries are not a consideration in licensing negotiations (they are treated as sunk cost). However, the pharmaceutical industry is an exception: "If we suppose that consumer demand for drugs is highly inelastic, then our model would suggest that the ceiling on the licensee's price range is far more likely to be defined by its in-house development costs than by its market constraints. Thus, the value of the transferred technology would be judged more in terms of the supplier's sunk R&D expenditure, on the assumption that the prospective licensee would incur similar development costs".

An extensive legal analysis of compulsory licensing provisions and practices in the drug industries in the U.K., Canada, France, Japan and Germany is due to Henry (1976). He emphasizes the contrast between the economically reasoned approach to calculation of royalties by the U.K. courts in the 1960's and 1970's with the "overly rigid flat-rate standard" employed in Canada.

In the U.K., the courts first established the research cost element, typically by reference to the ratio of the patentee's average annual expenditure on R&D to his average annual sales of pharmaceuticals arising from research activity. Secondly, promotional and administrative costs of the patentee in introducing the product, developing the market and servicing the drug were established. This consisted of the full cost of conducting clinical trails plus a weighted average of specified fractions of the cost of advertising, detailing and other marketing activities. To the sum of these costs was then added a profit markup (typically 22.5 %) to arrive at the final amount which the patentee should recover from sales revenues of the licensee. Moreover, the final royalty percentage was sometimes "uplifted" in anticipation of the price reduction which would result from competition by the licensees. Henry (1976, p. 330) believes that the profit allowances in compulsory licensing cases have been greater than they usually would be in cases of voluntary licensing. He notes, however, that without compulsory licensing the patentee would not necessarily choose to license anyone and would instead reap monopoly profits associated with inelastic demand for some drugs.

While in the U.K. the research component of cost in compulsory licensing calculations was based on all research in relation to all sales of drugs resulting from all research, in Canada the royalty is supposed to provide "due reward for the research leading to the invention". In practice the research component of the royalty in the U.K. averaged about 10% of sales, while in Canada it has been "nearly non-existent" (Henry, 1976, p. 340). In addition, no allowance is made for the cost of development of the market, borne by the patentee.

The U.K. procedure was designed to approximate the damages caused to the patentee, while the Canadian approach is to determine the value of the use of the patent to the licensee. The usual magnitude of the royalty rates assessed by Canadian courts has been 4% on dosage form or 15% percent on bulk sales. Henry (1976, p. 350) believes that the flat-rate Canadian approach would be "inadequate in a more industrial, research-oriented country". At the same time, the U.K. practice was deficient in that it did not consider whether the patentee was already adequately compensated or whether the licensee might be penalized simply because the patentee chose to spend an unreasonable amount on R&D.

3.4.4 Innovation and Competition

One theoretical argument bearing on the issue of price competition and industrial R&D spending is Feldstein's (1969) demonstration that the higher the equilibrium price elasticity of demand, the lower will be the ratio of R&D to sales. Thus, government policies to increase demand elasticity may also decrease R&D spending by firms. For example, compulsory licensing would decrease the R&D-to-sales ratio in two ways: First, the impact of research on sales would be diminished by the requirement to share information through licensing; and, second, the presence of additional firms selling the same product would increase the price elasticity of demand for the original brand.

The vast empirical literature on Schumpeterian competition and the relationship between market structure (as measured by the concentration ratio) is much less clear cut.[5]

If imitation is costly, the inventor can capture the benefits of his innovation. For the case of process innovation, Arrow (1962) argues in a classic article that incentives for innovation under these conditions are stronger in competitive markets than under monopoly, since the monopolist views his preinvention profits as a part of the opportunity cost of innovation. Demsetz (1969) shows that a monopolist has an incentive to spend a larger absolute amount on innovation when account is taken of the "normally restrictive" level of output under monopoly. Shrieves (1978, p. 332) asserts that the ratio of R&D spending to sales remains higher under competition, even when the adjustment suggested by Demsetz is made. Dasgupta and Stiglitz (1980) point out that Arrow's contention appears to be based on a single firm in isolation, and that it disregards the effects of interfirm rivalry on total industry R&D spending.

Empirical studies of the relationship between innovative activity and market structure have been summarized in extensive analytical surveys by Kamien and Schwartz (1975) and by Scherer (1980, Chapter 15). The bewildering variety of their findings includes the following observations: Inventive output is not systematically related to variations in market power (Scherer, 1965). The relationship is complex, since market power (as measured by industrial concentration) tends to coincide with the availability of technological opportunities in the respective industries (Scherer, 1967). Concentration influences research spending jointly (interactively) with product differentiation (Comanor, 1967). Concentration significantly raises R&D intensity in industries producing material inputs and consumer goods, has a weak influence in industries producing nonspecialized producer goods, and has a marginally significant negative influence in industries producing specialized durable equipment (Shrieves, 1978). And the regression coefficient of the concentration variable is significantly negative for "technology-rich" Canadian industries, but is not significant elsewhere (Globerman, 1973).

A fundamental theoretical challenge to the methodology of existing econometric research was recently published by Dasgupta and Stiglitz (1980). Their point of departure is the argument that, except in the short run, both market structure and inventive activity are endogenous, since both depend on such factors as research technology, demand conditions, financial market conditions, and the legal and institutional structure, including patent rights. The degree of industrial concentration, therefore, should neither be treated as given, nor as causally related to innovative activity.

Both the above authors and Loury (1979) observe that much of the published literature on this subject represents a partial equilibrium analysis of the behaviour of individual firms under various degrees of industrial concentration. In markets characterized by rivalry, however, each firm's R&D effort also depends on the anticipated response by competitors. In addition, the behaviour of the aggregate R&D spending by all firms in the industry cannot be simply inferred from the behaviour of a "typical" firm indicated by microeconomic models. While such models may indicate that rivalry reduces the R&D effort by each firm, the number of firms engaging in R&D may increase, and so may the total amount of the industry's R&D spending. R&D rivalry produces some winners and losers, some changes in the distribution of market shares, and thus it also effects changes in the industrial concentration.

Several other theoretical models and considerable empirical evidence suggest that the relationship between R&D activity and industrial concentration may be nonlinear. Finally, some authors have argued that the concentration ratio is not an adequate measure of the degree of competition or indeed an appropriate characteristic of market structure.

The existing literature on the tradeoff between incentives for innovation and competition (and resulting lower prices) suffers from a major conceptual deficiency (Comanor, 1984, pp. 100-102): Attention thus far has been directed at the level of returns to industry research rather than at the level of innovation. The elasticity of supply of innovation with respect to the rate of return on innovation (and, ultimately, with respect to policies influencing this return) has been neglected. If this supply elasticity is low, then policies resulting in a reduction of returns to innovation may not be costly to society. The second neglected problem has been an analysis of approaches to financing pharmaceutical R&D which should not require a restraint on competition or higher prices for existing products. In other words, given the public-good characteristic of R&D, the options of supplying pharmaceutical R&D publicly or subsidizing private pharmaceutical R&D have not received adequate attention.

4. CANADA AS A LOCATION FOR PHARMACEUTICAL R&D

4.1 Introduction

One recent assessment of Canada's propects as a location of pharmaceutical industry has been formulated in a "Statement of Concern Regarding the Pharmaceutical Industry in Canada," issued in late 1982 and supported by 14 Canadian associations, among them the Canadian Medical Association, the PMAC, a number of associations of pharmacists and pharmacologists as well as the Deans of pharmacy. It expresses concern with a range of developments, including the following: loss of jobs in pharmaceutical marketing and research; decreased investment in physical plant, resulting from the poor perceived investment climate in Canada on the part of the multinational pharmaceutical companies; increased reliance on imported pharmaceuticals, possibly raising issues of national security; decreased ability of the Canadian industry to handle technology, including transfer from abroad and transfer from university laboratories; increased potential for drug lag, since lower rate of return in Canada leads to delays in introduction of new products as compared to other countries; damage to Canada's international reputation resulting from compulsory licensing policies which amount to weakening of property rights to new technology.

The majority of these concerns are intimately related to the factors considered in the multinationals' decision-making on international location of R&D activity, reviewed above. In what follows, Canada's ranking with respect to the most important determinants of location of industrial pharmaceutical R&D is evaluated in light of the available evidence.

4.2 An International Perspective

Among the most important factors considered in selecting a country as a location of R&D facilities are: political stability, size and quality of the local scientific community and the past record of successful innovation. Of secondary importance are access to ancillary services, cultural compatibility with the home country and relative costs or R&D inputs. Brustall et al. (1981, pp. 71-72) conclude, on the basis of intensive interviews with industry executives and other evidence that these criteria heavily favour the U.S., U.K. and Germany. Special cases are: India, which has a large and well-established scientific community in addition to low cost; Australia, because of highly creative scientific personnel, large veterinary products market and access to unique plant and animal products; and, Canada, which, in their assessment "shares some of these advantages."

Location of development, especially of clinical testing, is determined by the requirement to have the clinical studies conducted at low cost in countries with high standards of medical practice. These criteria favour mainly the developed countries (small or large) with similarities in medical practice. Canada clearly figures prominently close to the top of any such list.

The standing (vitality) of the host nation's scientific community determines its ability to attract qualified manpower and financial resources and the perception of the nation as a centre of reserch. The R&D intensity of the industrial sector of the economy is perhaps even more important, since it generates skills and attitudes required in the application of science.

Two additional sectors are relevant: First, universities, hospitals and medical research institutes might represent an alternative source of pharmaceutical innovation. Second, the chemical industry generates expertise which can readily be transferred to pharmaceuticals and also provides a source of pharmaceutical raw materials. Burstall et al. (1981, p. 213) attribute the weakness of both Canada's and Australia's pharmaceutical industry, in part, to the nature of their chemical industries which they describe as "abnormally small and undifferentiated."

In an attempt to make an over-all assessment, Burstall et al. (1981, p. 98-100) classify the pharmaceutical industry in a cross-section of OECD countries according to two measures: absolute size and international competitive strength measured by the ratio of new exports to total production in 1975. Canada was classified in the "medium" category along both dimensions, together with Australia and Belgium. While internationally comparable data on Canadian innovative performance was not available, it was assessed as "low or negligible." Overall, Canada, together with Australia, Norway, the Irish Republic and Spain was classified as a "low-capacity country." This category is comprised of nations with "small undiversified local enterprises whose activities are largely imitative. Their pharmaceutical industry is dominated by foreign multinational companies. Their prospects of developing a viable indigenous pharmaceutical sector, actively engaged in international operations, are very limited."

4.3 Policy Environment

4.3.1 Introduction

A key characteristic of the Canadian R&D policy environment is the smallness of the Canadian economy. The worldwide sales of the pharmaceutical industry in 1980 are estimated at U.S. $22 bill. (Egan et al., 1982, p. 4), the Canadian sales reported by Statistics Canada were Can. $1.4 bill. Worldwide R&D outlays in the same year were estimated at about U.S. $2 bill. (Egan et al., 1982, p. 4) while the Canadian R&D expenditures reported by Statistics Canada were Can. $ 50 mill.

The problem of small open economies in the area of innovation and R&D policy derives from several aspects of the economics of R&D and innovation: First, the public good characteristics of new knowledge which result in incomplete appropriability of the results of R&D. (The analogy at the level of a firm is the issue of incentives to innovate by a monopolist vs. a competitive firm). Second, the literature on the relationship between firm size and innovation, while not conclusive, suggests, at the very least, that a minimum threshold firm size is required for successful innovation. Small economies, by definition, are unlikely to have many such firms on their territory and can thus be a priori expected to register a lower level of innovative effort. Third, one of the strongest determinants of location of research activities by multinational firms is the proximity to the primary markets. Small economies are at a disadvantage on this score as well.

From the point of view of maximizing social welfare, the objective of innovation policy should be to maximize access to new technology, regardless of its source. In reality, political considerations and non-economic objectives (such as "quality of the labour force mix" understood as a requirement that certain percentage of a country´s manpower be composed of scientists and engineers) make it necessary to consider the location of R&D activities as well.

Additional public policy concerns arise when the multinational corporations located in a particular country pursue discriminatory policies dictated either by their global profit maximization strategies or by the pressure of governments of their home countries. Under these conditions, the foreign parent companies may not provide their overseas affiliates with access to all of their latest technology, or may do so at high cost or with restrictions. It is also relevant whether the technology imported through intracorporate network requires more or less adaptation (at higher or lower cost) than technology imported independently from non-affiliated firms abroad.

4.3.2 Government Policies in Support of R&D

Viewed in an international context, Canada possesses certain key prerequisites for sustaining an innovative pharmaceutical industry (tradition of scientific research, developed industrial sector, some strength in fine chemicals). In discussing the range of policy options open to such small countries, Burstall et al. (1981, pp. 234-235) define two possible broad strategies in promoting innovative capacity for pharmaceuticals: First, the "low control" option which amounts to inducing multinational companies to establish research facilities in the country. Second, the "high control" option of building up an indigenous research capacity.

The first strategy may require such policy tools as a relaxation of safety controls in new product introduction, price policy permitting high profit margins, strengthening of property rights, including length of patent protection, etc. These policies may, however, take a long time to produce results, may not work at all, may attract only specialized research functions rather than full range of innovative activity, would raise the price of drugs and possibly reduce their safety. The second strategy may require a major shift in national priorities and substantial political commitment, as well as a long period of time before any results could be expected.

Government policy instruments (subsidies, tax support, trade policies, etc.) are more likely to succeed in influencing the multinational companies' decisions where the national market is large or where the company is already deeply committed. In other cases, it may choose to withdraw rather than submit to external pressure. For example, de Vos (1983) documents a number of instances from several European countries where the foreign-owned multinationals in the microelectronics industry did not accept the host country government grants in support of R&D. The usual grounds for rejection were that the associated administrative burden was "onerous", or that the requirement that results be exploited within the country was "unacceptable", or that the government inspection of the company books as a condition of the grant constituted "undue government interference."

In the context of the OECD countries, Burstall et al. (1981, p. 174) conclude that the multinational pharmaceutical companies located in Canada have not benefited significantly from government incentives for R&D. One reason may be that their product development activities are undertaken outside the country and are thus not eligible for the development-oriented government programs.

Receiving government support for R&D may have two contradictory effects on company-financed R&D. On the one hand, the firm may use up government money for projects it would otherwise finance itself. This may, in part, be necessary since the firm's physical capacity to perform R&D is limited. On the other hand, it is possible that the results of government-supported R&D raise the profitability of private R&D. As a consequence, the firm will add company-financed projects to enhance these benefits further.

A particular problem arises when most of the top R&D performers are foreign-based multinationals. Government policy toward R&D then has to cope with matters such as the following: First, in administering financial assistance to R&D, e.g., grants and tax concessions, the issue of "incrementality" (assurance that the R&D project supported by government would not have been undertaken without such support) acquires a particular urgency since government funds may end up subsidizing foreign shareholders. Second, the conditions the host country governments may wish to impose on recipients (provision of information on the firm's activity, restrictions on licensing abroad, domestic manufacturing) may not be acceptable to the multinationals, rendering thus the government efforts ineffective.

The first issue is of particular relevance to Canada. A recent examination of government incentives for R&D in some 20 countries (McFetridge and Warda, 1983) concludes that the fraction of industrial R&D supported by subsidies in Canada is the highest of all the countries examined. When both subsidies and government R&D contracts are taken into account, Canada ranks second only to Singapore.

McFetridge and Warda (*ibid*., p. 91) suggest that "it is not necessarily in Canada's interest to provide for substantially more generous tax treatment of R&D than do other industrial countries. In a world where technology can be developed in one location and used without compensation in many others, one may appeal to the taxpayers of a small country to provide a high level of support for R&D on altruistic grounds. An appeal based on self-interest would be much more difficult to sustain." They further point out that tax advantages need not necessarily attract the "footloose" R&D activities of foreign-owned firms. Depending upon the relative tax rates in the host country and the home country and on the form in which the subsidiary transfers its profits to the parent company, it is possible that the reduction in tax liability by means of tax concessions for R&D in the host country may be offset by an increased tax liability in the home country. In other words, the multinational has no incentive to relocate its R&D facilities to the host country in order to minimize its global tax burden.

A number of recent U.S. studies analyzed the aggregate relationship between the level of R&D expenditures financed by the U.S. federal government and privately-financed R&D expenditures. A brief review by Mansfield and Switzer (1984, p. 563) shows estimates ranging between 7 and

20 cents of increase in privately-financed R&D expenditures for every one dollar of increase in government-financed R&D.

Howe and McFetridge (1976) investigated this issue with a sample of 81 Canadian firms in the electrical, chemical, and machinery industries during the period 1967-71. The Canadian-owned electrical firms were found to have increased the volume of own funds invested in R&D by more than the amount of the grant, while the foreign-owned firms raised their own R&D investment by less than the amount of the grant. In the other two industries, the hypothesis that receiving a grant does not change the total R&D expenditures of a firm could not be rejected. In no case, however, were these grants deemed to be simply replacing (substituting for) own funds.

Shrieves (1978), using data from a sample of 411 U.S. firms in 1965, found an inverse relationship between R&D intensity and the percentage of R&D financed by government. (His multiple regression coefficient on this variable was negative and statistically significant at the 0.05 level.) Nadiri's (1979) analysis of a sample of 11 U.S. industries during the period 1958-75 showed a positive, statistically significant effect of the growth of the publicly financed stock of R&D on the private stock of R&D in total manufacturing and in durable goods industries. However, the effect was found to be negative and statistically significant in nondurables.

Longo (1984) reports the results of regression analysis on firm data (447 observations) spanning 24 Canadian three-digit industries that had R&D to sales ratio of 0.5% or greater in 1979. Government grants in support of R&D were found to have a positive effect for Canadian firms in the sample, but the own privately-financed R&D expenditures of foreign-owned firms were found not to be responsive to government grants.

Mansfield and Switzer (1984) investigated this relationship with a set of interview data pertaining to energy-related R&D of 25 firms belonging to four different industries (electrical equipment, petroleum, aerospace, chemicals). They asked senior executives to estimate the effect of a change in federal funding on their firm's company-financed R&D. Consistent with the aggregate studies mentioned above, their results indicate complementarity: For every dollar of increase in federal support, the sample firms would increase their own financing of energy R&D by 6 cents in each of the first two years, with no effect after that. For each dollar of federal support reduction, they would reduce their own financing by 25 cents in each of the two following years and by 19 cents in the third year.

These results, however, conceal a considerable amount of inter-firm variation. The over-all complementary relationship between private and government funding is the result of responses of a small number of firms, with the vast majority exhibiting very little or no response. It is also relevant whether the R&D project was formulated largely by the government or whether it was conceived principally by the firm. A statistical test confirms that the probability of privately-financed spinoffs resulting from government supported R&D is 20-30% higher for projects of the second type.

4.3.3 The Impact of Foreign Ownership

Penetration of a national economy by multinational companies may enhance or weaken the indigenous industry: If the domestic industry is highly fragmented, it will be weakened as a result, especially if substantial economies of scale are present. Similarly a deliberate policy of centralizing R&D on the part of multinational companies will reduce the host country's scientific capacity.

If these policies prevail, one implication of a high degree of foreign ownership will be low R&D-to-sales ratio in the host country's industry due to "invisible imports" of technology via multinational corporations. Burstall et al. (1981, p. 173), commenting on the low level of pharmaceutical R&D in Canada observe that "technology and the results of innovation from parent corporations have been so readily available and so economically attractive in the short term that the growth of national innovative technological capacity has been severely inhibited."

In an analysis of the determinants of R&D intensity in a cross-section of countries, Palda and Pazderka (1982) obtained significant negative coefficients on a variable representing the degree of foreign ownership in the particular industry in three out of seven industries (among them pharmaceuticals) for which such regression was estimated, lending support to the "invisible imports" hypothesis.

Palda (1984, Ch. 6), using methodology previously developed by the Ministry of State for Science and Technology (MOSST), provided an estimate of the amount of invisible R&D imported into Canada via multinational corporations. For the year 1981, his calculations indicate that in the pharmaceutical industry such imports amounted to 30% of domestic R&D. This contrasts with 26% for pulp and paper and 200% for transportation equipment.

In interpreting these numbers, one should be aware of some of the problems with the methodology developed by MOSST. It assumes, first, that (foreign) susidiaries should be supported by the same R&D-to-sales ratio as the parent company. Second, this ratio is applied uniformly to all foreign subsidiaries located in Canada, even though the percentage of equity participation by foreign parent companies varies across subsidiaries. Third, no information is available on the quality of the knowhow transferred abroad, as compared to the knowhow available to the parent company.

Palda (1984, Ch. 5) also addressed the definitional and measurement problems inherent in the standard characteristics of technological intensity, such as the R&D-to-sales ratio. For selected industries, he attempted to estimate the contribution of immediate upstream suppliers′ research to the industries′ technological intensity. For the Canadian pharmaceutical industry, this contribution amounts to only 3.3% of its own intramural R&D. This contrasts with the pulp and paper industry where the estimated contribution of immediate upstream research is 62.3% of the industry′s own intramural R&D.

Hewitt (1984) inquired into the specific factors determining the percentage of global R&D spending the U.S.-based multinational pharmaceutical companies locate in Canada. His regression equation estimates the determinants of the variation in percentage of worldwide R&D

located in Canada by a sample of 18 companies with manufacturing subsidiaries in Canada. (Pooling of data for the years 1973, 1975 and 1977 yielded 49 usable observations).

One group of independent variables control for such characteristics of the sample firms as their global organizational structure, length of time since manufacturing operations in Canada were established, worldwide R&D intensity of each firm and the share of the firm's Canadian expenditures financed by Canadian government grants. For two observations, corresponding to American Home Products and Merck, Sharp & Dohme, a dummy variable was included, representing the fact that these two firms acquired Canadian companies with established R&D capabilities in pharmaceuticals. (The former acquired Ayerst McKenna and Harrison in 1943 and the latter acquired Charles E. Frosst in 1965).

Another group of independent variables is designed to capture the special characteristics of pharmaceutical R&D. First, it is hypothesized that the parent company's orientation on discovery, as opposed to clinical research, reduces the share of its R&D located abroad, since clinical testing is easier to decentralize. Next, the larger the fraction of the company's global new product innovations marketed in Canada, the higher the fraction of its worldwide R&D located in Canada. The importance of Canada in the company global sales is postulated to have similar effect. The corporate mix of R&D is supposed to measure both the willingness and ability to decentralize clinical R&D. The new product innovations and size of the Canadian market measure the relative attractiveness of Canada as a location for clinical R&D.

Hewitt also attempted "the first rigorous statistical test" of the hypothesis that the introduction of compulsory licenses to import pharmaceuticals protected by Canadian patents negatively affected location of R&D activities in Canada. Based on PMAC documents, on academic analysis of PMAC lobbying efforts and on statements of government officials, he postulated that this type of industry reaction constitutes "retaliation" motivated by concerns for the integrity of the patent system, worldwide marketing scheme for drugs and worry that other countries might follow Canada's example to reduce their prices of drugs. Empirically, the magnitude of this effect is measured by the percentage of sales each sample company lost to compulsorily licensed substitute products.

Of the estimated regression coefficients, two are significant at the 99% level: the dummy variable indicating takeover of Canadian firms with existing R&D facilities and the variable measuring impact of compulsory licensing competition. The former suggests that "it is presumably easier and cheaper to maintain rather than initiate a Canadian R&D capacity." The latter is consistent with the "retaliation hypothesis" and with the emphasis pharmaceutical companies place on patent protection. Two other regression coefficients are significant at the 95% level: the company's share of total global R&D devoted to discovery R&D is indeed found to be negatively related to the dependent variable, confirming that discovery research is not as easily decentralized as clinical testing. The percentage of the company's worldwide new product innovations marketed in Canada obtains a positive coefficient as hypothesized.

This regression methodology may be subject to critism for omitting some potentially important explanatory variables. Among them are a measure of profitability or past success of Canadian subsidiaries relative to the parent company or affiliates located elsewhere as well as relative costs of doing R&D on different locations. Hewitt implicitly rejects such criticisms by postulating that firms do not behave like fully-informed profit maximizers; rather, they are modelled as imperfectly-informed, slow-learning satisfiers.

The "retaliation hypothesis" is one interpretation of the negative correlation between compulsory licensing and share of R&D activity located in Canada. The economic connection between profits lost in Canada because of licensing and the volume of global R&D spending by the multinational corporation affected is not easy to make, since the Canadian market represents only about 2% of the world market of the research-intensive pharmaceutical industry. It is thus sometimes argued that Canadian consumers of pharmaceuticals should contribute to multinational research efforts on ethical grounds.

For example, Eli Lilly (1984) in its submission to the Commission expresses the opinion that "it would not be responsible to shift Canada's share of R&D on other nations since Canadians benefit from new drugs more than most other nations because of advanced medicare system." Similarly, Friedman (1981), in a study commissioned by the PMAC observes that, while Canada could assure itself of a free ride by doing no drug research, it would be inappropriate for two reasons: First, it would amount to shifting its share of financing of R&D to other nations and, second, such a policy would not be "free of cost to Canadian interests," since it would have a "depressing effect on a variety of business decisions, particularly those related to maintaining or expanding factories, research facilities, and employment in Canada."

The much discussed instance of the closing of the research establishment of Ayerst McKenna Laboratories in Montreal, early in 1982, with the consequent loss of 270 research jobs has been attributed to a number of causes. While compulsory licensing and provincial substitution laws are listed among them, their importance relative to the others has never been clearly specified. The other factors include the desire to consolidate research activity in the home country, recruitment difficulties as a result of Quebec language laws, the Constitutional debate and perceived risk of political instability in Canada, etc. (see e.g. Garner, 1982).

The results of a survey conducted some time ago by the U.S. Pharmaceutical Manufacturers Association (PMA, 1972) provide some insight into the implicit weights attached to locational decisions made at the headquarters of multinational corporations. Although they relate to the location of manufacturing operations, they are relevant to the location of R&D facilities as well.6)

The firms were asked to evaluate which among ten factors were important in deciding upon establishment of foreign manufacturing operations. By far the most important stated reasons were "tariff and trade restrictions" (95 percent of answers), followed by "legal and other requirements for local production" (85 percent of answers) and "better servicing of existing work"

(81 percent of answers). Tax benefits were important for only 33 percent and of minor importance for 52 percent; access to scientific research laboratories and other intangibles was judged as "inconsequential" or of no importance by 48 percent of respondents. The degree of patent protection in the host countries is not explicitly mentioned among the most important determinants, although it may well be a part of the "intangibles" which received a rather low priority rating.

Recent trend has been toward a relative decline of domestic innovative capabilities in the small capacity countries, including Canada. The most likely cause seems to be the rising cost of innovation, rather than the multinational system of the industry operation. As noted by Burstall et al. (1981, pp. 206-208), historically, around the turn of the century, only a few German and Swiss dyestuff companies applied their established research expertise to the synthesis of pharmaceuticals. The development of a research-based pharmaceutical industry in the U.S. was given a major impetus in the late 1930's with the exodus of scientists from Germany and the establishment of Swiss subsidiaries in the U.S. Further impetus was provided by the growth in demand for anti-infective agents needed for the war effort.

The presently observed differences in innovative capacities of the various national pharmaceutical industries were essentially established during the 1950's. Since multinational activities of the large firms at that time were limited, Burstall et al. (1981, p. 204) infer that the "multinational system of organization cannot therefore have caused these differences; at most it may have maintained them." The long-term stability of the dominant position of certain nations (and large firms) is also more likely due to the barrier to entry arising from escalating costs of drug development than to the multinational system of industry operation.

The trend toward decentralization of R&D activity away from the U.S., discussed in Section 2.2.2 above could, of course, be interpreted as a component of a long-run equilibrating mechanism: The World War II disruption in educational system and research establishment in European countries have been in the process of rectification over the past two decades and the shift of R&D toward Germany and some other European countries is a sign that these countries are returning to their traditional equilibrium positions. A detailed analysis of the causal factors behind such shifts should take a long-period perspective (e.g. 50 years or more), encompassing the War as a disruptive factor and recognizing that it takes a long time to re-establish scientific infrastructure, including the university system.

4.3.4 An International Pespective

Recent policy developments in a number of countries seem to indicate a trend toward strengthening of patent protection for pharmaceuticals. For example, in 1976, Japan revised the patent law to permit patents on compounds per se (including pharmaceuticals). In 1978, the Italian Constitutional Court declared unconstitutional the position of the Italian patent office which refused to grant patents on pharmaceuticals. (While Italy had no patent protection before 1978, its drug prices were comparable to those in other countries). Also in 1978, U.K. eliminated a compulsory licensing provision which served as a model for s. 41(4). This licensing provision had been used intermittently and had a limited impact. The U.S. Patent Restoration Act also falls into the general category of policy moves strengthening patent protection for pharmaceuticals.

Changes in the same direction have recently taken place in the area of "parallel importing" of pharmaceuticals in Europe as well.[7]) The EEC Commission in the past supported "parallel importing" of drugs as a means of promoting the development of a common market in medicines. The judgements of the European Court rendered ineffective the patent and trademark infringement actions brought by research-oriented multinational pharmaceutical companies. This was the case both when the parallel importer sold the product under the original trademark and when he repackaged it (to satisfy local prescribing habits) and sold it under an alternative trademark of the same manufacturer. This practice was permitted even if there were differences between the products sold under the different trademarks, as long as the therapeutical effects were "substantially the same", the fact of repackaging was indicated and the trademark owner was notified in advance. The Court ruled in favour of the parallel importers whenever it could be shown that the use of the trademark against parallel importers would "contribute to an artificial separation of national markets."

Recently, however, the German Federal Supreme Court reversed this practice in adjudicating a dispute between Hoffman-La Roche and Centrafarm. It ruled that in producing different packages for different markets, and charging different prices, Roche was "guided by legitimate marketing considerations." Even if these marketing practices created barriers to trade among the ECC member countries, Roche cannot be forced to abandon them. Similarly, Glaxo achieved a favourable settlement in its action against parallel importers of Ventolin in the U.K. The parallel importer was obliged to disclose a list of all pharmacists to whom the imported product had been supplied.

The British government proposed an amendment to the regulations governing importation of medicines. It would require parallel importers who bring in small quantities of a large number of products to obtain a license and pay a license fee for each product. This requirement would impose a larger financial burden on parallel importers in comparison with authorized agents of the pharmaceutical companies who deal in large volumes of smaller number of drugs.

Over-all, in an international context, Burstall et al. (1981, pp. 57-58) conclude that, in the major producing countries, the needs of the pharmaceutical industry had little influence on government research policies. France is a partial exception since the government attempted to promote large indigenous pharmaceutical companies by means of fiscal incentives and concessions. The success of the pharmaceutical industry in small countries, such as the Irish Republic, is typically due to incentives which are general in nature, rather than explicitly directed at this industry.

4.4 The Relative Strength of the Science Base in Canada

Several authors, among them Grabowski and Vernon (1982, pp. 305-313) criticize the tendency in much of the existing literature to view the relative contributions of the private industry vs. government laboratories and universities in a "competitive" perspective, i.e. attempting to show that one, rather than the other, sector contributes more. They present a substantial amount of U.S. case studies and other evidence to emphasize the cooperative nature of this relationship.

In order to provide a Canadian perspective on this issue, we have asked the Deans of Faculties of Pharmacy at several Canadian universities to express an opinion on the relative strengths and weaknesses of the relevant scientific disciplines as well as other factors which might affect the location of pharmaceutical industrial R&D facilities in Canada. Three Deans responded; a summary of their replies follows.

The Deans agreed that a number of scientific disciplines are relevant, among them: Clinical Pharmacology; Medicinal Chemistry; Toxicology, Pharmacokinetics, including Drug Disposition and Metabolism; Physical Pharmacy and Pharmaceutics. In addition, the strength of all basic science departments in the Faculties of Medicine, but especially Physiology, Biochemistry and Microbiology is of consequence.

By way of an overview of the activities of pharmacology departments, Dr. Dennis Johnson, Assistant Dean of Medicine (Research) and Acting Head of the Department of Pharmacology, University of Saskatchewan, writes:

> "There are many strong pharmacology departments at universities across Canada. The strength of these departments, I suspect, can be measured by the amount of external funding received from such sources as the Medical Research Council of Canada and the private funding areas. Some of the departments have been in existence for several decades. Others are approximately a decade old. The amount of research activity in the pharmacology departments is highly variable depending in part upon teaching loads, which also varies widely across Canada. With respect to research activity, it should be made clear to the Eastman Commission that the type of research conducted in a pharmacology department is primarily directed towards developing an understanding of normal physiology and how drugs work as opposed to a product orientation. That is, the goal of most fundamental researchers at universities is not product oriented. This then differs considerably from the type of pharmacological research that would be undertaken in a pharmacology laboratory within the pharmaceutical industry. However, the Eastman Commission should understand that the development of products is based on fundamental concepts that have, by and large, emanated from basic science departments in universities. Thus, the concept of alpha and beta receptors led to the development of drugs that are effective on the receptors postulated by these concepts."

and, commenting on disciplines other than pharmacology:

> "During the past decade, there has been a great increase in the expertise and research activity in Colleges of Pharmacy in all of these disciplines. I believe a number of health science institutions in Canada now posses the research expertise, equipment and facilities to undertake research in all facets of discovery and development of a pharmaceutical product."

The following specific, discipline by discipline, assessment was offered by Dr. John W. Steele, Dean, Faculty of Pharmacy, University of Manitoba:

> "I would suggest that only pharmacokinetics (including drug disposition and metabolism) is relatively strong in Canada. There are several centres of excellence, some of which are of international level. Physical pharmacy is weak and pharmaceutics is also no better than average and probably should also be regarded as weak. Pharmacology, for the most part, is taught in faculties of medicine and only occasionally in faculties of pharmacy (for example U.B.C.). It is therefore difficult for me to decide whether or not pharmacology is comparable to the rest of the world. I believe that pharmacology in faculties of medicine is reasonably strong and there are indeed several centres of excellence in Canada. Clinical pharmacology would normally be centered in faculties of medicine also. Some pharmacy-based individuals are undoubtedly doing clinical pharmacology research but usually in conjunction with members of the faculty of medicine. I believe the relative strength of this sub-discipline is good but not outstanding. In general I believe the numbers of persons involved in clinical pharmacology is much less than it might be. I believe that toxicology is relatively weak in Canada and medicinal chemistry is about average."

Both Dr. Johnson and Dr. J.L. Blackburn, Dean of Pharmacy, University of Saskatchewan, made a comment on the level of industry/university/government interaction in pharmacological research in Canada:

> "To my knowledge there is very little interaction between basic pharmacology departments and the industry in Canada with respect to the sponsorship of fundamental research. However, I do think that there is a considerable amount of collaboration in the development of new drug products. This collaboration may not necessarily be between basic pharmacology departments, but also between the various departments in clinical medicine. I know of very little interaction of a tripartite nature involving industry/university/government......
>
> I also believe there is a much greater amount of collaborative research between the industry and colleges of pharmacy in both the United States and Great Britain than there is in Canada."

Dr. J.A. Bachynsky, Dean, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, supplied the following examples of specific research collaboration between the industry and the University of Alberta: Research on a diagnostic test for breast cancer, sponsored by Summa Biomedical Canada; contract research into the synthesis of beta lactam conducted for Bristol Laboratories; research into a radiopharmacy kit sponsored by Frosst Radiopharmaceuticals of Canada. In addition, the University of Alberta now owns a biotechnology firm, Chembiomed, and is negotiating joint research with biotechnology firms in Toronto and in Japan.

A rough quantitative perspective on the strength of selected relevant scientific disciplines in Canada can be generated from an inspection of data on citations of scientific articles. A summary of this information for Canada, in the degree of disaggregation made possible by the original source of the data, is provided in Table 4-1. (The full set of this data, for selected major countries and for all intervening years between 1973 and 1980 is in the Appendix Tables.)

Table 4-1: Science Citation Index, Percentages of World Total, Canada

Field of Science	Year 1980	 1973
Clinical Medicine - Pharmacology	3.94	3.16
- Pharmacy	1.36	1.51
Clinical Medicine - Total Field	3.57	3.33
Biomedical research - Total Field	4.00	4.56
Biology - Total Field	8.25	8.04
Chemistry - Total Field	3.27	3.84
Total of Above Fields	4.11	4.25

Source: Compiled from Appendix Tables. Original data source; CHI Research NSF Science Literature Indicators Data-Bank (held at the Science Policy Research Unit, University of Sussex).

The scientific fields listed in the table are clearly not equally relevant for pharmaceutical R&D; some represent an aggregate of very wide-ranging subfields of science (e.g. Biology). Given the data source, it is known that the coverage of the literature scanned in compiling the figures (some 2,000 journals) is somewhat biased in favour of English-language articles in general and U.S. periodicals in particular.

It is not entirely clear against what standard the above numbers should be compared; perhaps the share of Canada's pharmaceutical R&D in the global R&D spending in pharmaceuticals (roughly 2%) may be one possible yardstick. It would, however, seem that the impressionistic evidence reported from various sources about the strength of Canada's science base and thus attractiveness of Canada as a location of pharmaceutical R&D are borne out by the evidence.

As for the availability (rather than quality) of scientists in the fields of interest, various Canadian industry sources report a shortage of clinical pharmacologists and toxicologists. This, however, appears to be a world-wide phenomenon, detected also by Burstall et al. (1981, p. 89) who link it with the growing emphasis on drug safety in most countries.

The importance of the science base and its strength as a determinant of location of R&D activity is well established. For example, Burstall et al. (1981, pp. 208-211) categorized the OECD countries into three groups, according to the level of "national capacity for pharmaceuticals." It is evident from their cross-tabulations that the two key determinants of the ranking of countries according to this criterion are "national research intensity" and "size and quality of the national scientific community" (the third important determinant is "national wealth and size of the market").

Using a different methodology, Palda and Pazderka (1982) attempted to evaluate the importance of a similar set of variables for the R&D intensity of selected industries in a cross-section of countries. While the regression results for most of their variables are mixed, the one variable which shows a consistently positive statistically significant influence for all seven industries studied (including pharmaceuticals) is a measure of the strength of the "national science base."

4.5 Consequences of the Corporate Decision-Making Process

The standard economic model of the firm views the multinational corporation as locating its facilities around the world so as to maximize the net revenue from serving any given market (e.g. Caves, 1982, p. 198).

If the multinational's intangible output could be transferred costlessly among the various plants, the R&D laboratory would be put in the lowest-cost location. However, R&D activity is pulled away from a single "ideal" location by a number of influences, among them the requirement of continuous exchange of information between manufacturing facilities and R&D, need for close interchange with top corporate management, economies of scale in R&D, government policies in other countries encouraging R&D on national territory, etc.

The economic model of the decision to locate R&D facilities in different national markets thus assumes (explicitly or implicitly) that the multinational headquarters gather all the relevant information, assess the comparative advantage of the various potential locations and decide where the incremental resources destined to be spent on R&D should be directed. The management of Canadian subsidiaries of multinational pharmaceutical companies in their briefs to the Commission seems to consider this view of the world as incomplete for several reasons: First, the setting for the decision process at the level of multinational headquarters is not a selection from a range of opportunities assembled at a point in time, but each proposal from a subsidiary is evaluated individually, as and when it is presented. Second, the past performance of the competing subsidiaries (both the R&D and profitability performance, but primarily the latter) is viewed by management as the key factor. Third, information is incomplete and imperfect; to overcome uncertainty, multinational management resorts to such informational inputs as its assessment of the "investment climate" in the host country (including patent protection), tax support for R&D, including past experience with the stability of such measures, etc.

This understanding of the decision-making process seems to be implicit in much of the argumentation of the Canadian management of multinational subsidiaries. The importance they attach to the last two factors in particular appears to be the main element in their opposition against compulsory licensing, generic substitution and policy changes. From this perspective, the attractiveness of Canada as a location for R&D has diminished.

Recent developments in the management of the R&D process within the major multinational pharmaceutical companies are characterized by a shift away from domination of the decision-making mechanism by research scientists towards greater emphasis on formalized project selection procedures (Wiggins, 1981). While in the 1960's, the two main factors (criteria) dominating the choice of research projects were medical need and scientific feasibility, the process has now become more quantitative, with more systematic attention paid to profitability considerations. In what follows, the potential implications of this shift for location of R&D activity in Canada are briefly explored.

Wiggins (1981, pp. 55-83) describes the sequence typically followed in the choice of research projects as follows: first, a member of the scientific team has an idea about potential future research, derived from a variety of sources, including the literature and professional contacts, but also, to a lesser degree, from marketing personnel, management clinicians, etc. He is typically given considerable latitude in formulating the idea and strives primarily to satisfy "medical need." Second, the idea is informally discussed around the laboratory to test, in a preliminary way, its validity. Third, a proposal is made to establish a formal research project.

Fourth, the potential projects are considered at an annual meeting and inputs are sought from: research chemists and biologists (to evaluate the potential pharmacological effects of a particular type and technical feasibility of production); clinicians (to seek input on clinical feasibility and probable clinical costs, estimate of overall costs, and likelihood of FDA approval); marketing department (to establish the drug's potential, marketability and "marketing franchise", i.e. its fit within the company's product line, contacts with prescribing doctors and the like); the R&D department (to assess its ability to handle the project and its synergism with existing research and product lines). The importance of considerations included at this stage has increased during the past 15 years as a result of the dramatic rise in the costs of clinical testing.

Fifth, each project is reviewed at least once a year, and the frequency of reviews increases as more resources are committed. Increasingly, continuing project funding is tied to the requirement that certain hurdles be met, e.g. achievement of certain goals by specified date.

Sixth, the key stage of the project is reached when the potential new product is introduced into humans. Testing on humans sharply increases the costs and an evaluation of prospects at this stage is essential. It includes an estimate of manufacturing costs, reassessment of the expected sales, review of the future requirements of clinical trials, and estimate of the prospects of approval by the FDA. If phase I tests show no adverse reactions, the prospects of the product reaching the market are very high.

A formal calculation of the rate of return on a new drug becomes feasible only after the clinical tests are completed. Before formal calculations become feasible, firms allocate resources to R&D projects and determine their R&D budgets with the help of rule-of-thumb relationships, such as the R&D to-sales ratio. Apart from coping with uncertainty, such rules also provide some stability in the employment of scientific manpower and other R&D inputs. The incentive to perform a formal rate of return calculation at this stage is enhanced because the subsequent stages of new drug development are associated with rapidly escalating R&D costs.

The main impact of the formalization of the project evaluation has been that the decision process resembles zero-based budgeting. Funding for successive stages of the various competing projects is decided upon the various criteria for prospects of future progress.

This recent management approach is in contrast with the practice in the 1960s when the usual practice was to set aside certain percentage of sales and R&D budget which the research scientists then allocated among the existing and newly formed projects with little input from other functional disciplines within the company.

Whether this change in R&D decision-making procedures works toward the advantage or disadvantage of subsidiaries of drug companies located in Canada is not certain. On balance, however, it would seem that the quantitative project evaluation approach is more favourable to their position. The determination of R&D budgets hinges, at least in theory, on the merits of of each of the competing projects (its potential contribution to the global earnings of the firm). The older system of rule of thumb determination of overall R&D budget with allocation to projects decided susequently and with limited range of informational inputs would appear to be more susceptible to subjective influences, not necessarily compatible with the maximization of global corporate profits.

5. CONCLUSION

The review of theoretical literature on hierarchy of corporate functions in Chapter 2 shows the existence of a strong interdependence between production and R&D activity. In the pharmaceutical industry, in addition, integration of production and R&D represents a method of extracting rent from patented products which is superior to licensing drug patents to others. Empirical evidence presented in the same chapter confirms that the international distribution of foreign direct investment is highly correlated with the distribution of overseas R&D activities of the multinational corporations.

Survey data show a trend toward decentralization of R&D activities by U.S.-based multinationals from the U.S. to other countries, more so in the pharmaceutical industry than in many others. Canada, however, has not benefited from this development; its share of both U.S. direct investment and of R&D spending abroad has declined. This seems to be the case for a broad cross-section of industries, pharmaceuticals included.

Discussion of the factors influencing international location of production and of R&D activities in the last two sections of Chapter 2 sheds some light on the reasons for this state of affairs. In the pharmaceutical industry (as in many others) economies of scale in production of bulk ingredients are pronounced. A large pharmaceutical multinational firm typically has only 2 or 3 such plants; large developed countries (among them the home country of the parent company) and countries with generous tax concessions are preferred locations. The manufacture of final dosage forms, on the other hand, is widely decentralized, in part due to a variety of licensing and import restrictions, marketing considerations, tax concessions, etc.

Among the factors influencing the location of R&D facilities, economies of scale again figure prominently. The critical mass for a research establishment in pharmaceutical industry is believed to be between 200 and 300 personnel. Economies in costs of services and overhead are believed to be significant, although the available econometric evidence is rather inconclusive: The earlier studies concluded that economies of scale in R&D were exhausted well below the obsrerved largest sizes, while more recent studies show constant or increasing returns to scale.

Other considerations in location of R&D facilities are the relative costs in the various locations, including tax concessions and other forms of government support for R&D, supply and quality and of R&D personnel, and policy factors, including drug safety regulations and testing requirements, etc. A brief examination of several studies of location of pharmaceutical research facilities within countries (U.K. and U.S.A.) show findings broadly consistent with the theory and evidence on international location: The most important factors are the proximity to the head office and to the main production unit. Somewhat surprisingly, proximity to other research establishments, such as universities, figures less prominently. Some decentralization of R&D activities has taken place of the past two decades; it has been more pronounced in the pharmaceutical industry than in most others for which the intra-country distribution of such facilities has been studied.

A long-standing issue in the literature reviewed in Chapter 3 has been the relative importance of industry laboratories versus other institutions as the source of new drugs. If it is the case that the industry's share is unimportant or that its effort does not yield major innovations, then policy measures such as compulsory licensing may reduce the total R&D spending, but not the flow of important new products.

While the specific numbers depend on the choice of weights describing the therapeutic or economic contribution of new products, the recent empirical studies show a large and growing role of the industry as a source of innovation. Within the industry, in turn, large multinational firms provide most of the new products in the "high technology" market, while the smaller firms operate mostly in the established, low-technology markets.

The tightening of regulatory standards for new product introduction raised the costs of pharmaceutical innovation and adversely affected the number of new product introductions. The problem of isolating the impact of regulation on product innovation from other factors, such as depletion of research opportunities, had not been fully resolved. Similarly, the extent to which major discoveries, as opposed to research leading to minor product differentiation, have been affected, is a subject of debate. It is reasonably clear, however, that the shift of innovative activity away from the U.S. (and, presumably, Canada), existence of the drug lag and reduction in the measured rate of return in the drug industry are related to regulatory changes.

The lengthy controversy regarding measurement of the rate of return in the industry and profitability of drug innovation is reviewed in section 3.3. The range of published estimates is rather wide and assumptions made in the various studies vary widely, but all available evidence points to a decline in profitability of drug innovation over the past two decades. Over the same period, however, pharmaceutical industry's R&D expenditures have been growing in real terms. This apparent inconsistency can be explained by lags in R&D decision-making process and availability of cash flows generated from sales of drugs introduced in earlier periods. In addition, rate of return on some new drugs is much higher than the observed average, thus providing a strong incentive for innovation, especially if pharmaceutical firms behave as risk-takers, consistently underestimating the risk of product failure.

The patent protection of new drugs, compulsory licensing and related policies have received a great deal of attention, since they are at the core of the fundamental public policy tradeoff between competitive prices of existing drugs and future flow of pharmaceutical innovation. The shortening of effective length of patents due to regulatory delays in particular has received attention recently: When the time value of money is accounted for, a simulation exercise shows, for example, that cutting the new product approval process by 1.5 years would reduce the payoff period for R&D from 19 to 14 years.

A survey of the evidence on licensing of pharmaceutical patents shows that in arm's-length transactions the royalty rates negotiated in voluntary licensing agreements are significantly higher in pharmaceuticals than in other industries. The Canadian approach to setting royalties in compulsory licensing cases at 4% of sales appears inadequate for two reasons: First, the level of the royalty is lower than would obtain in arm's-length transaction. Second, the uniformity of the royalty rate regardless of the costs of R&D and costs of developing the market for the new product further aggravates the distortion of of private incentives to do R&D.

As argued in Chapter 4, most of the criteria for choice of location of R&D by multinational pharmaceutical companies favour the U.S., U.K. and Germany. Countries usually listed as "special cases" are India (with a large scientific community and low cost), Australia (with creative scientific personnel, large veterinary market and unique plant and animal products) and Canada (with some of the above advantages as well as high standards of medical practice and high reputation of clinical testing facilities). Among the OECD countires, the competitive strength of Canada's pharmaceutical industry is classified as "medium"; its innovative performance is described as that of a "low-capacity country".

Among the causes of the weakness of the innovative potential of the industry in Canada are the small size of the market and absence of firms with minimum efficient size of laboratory. Both of these factors are among the key determinants of decentralization of R&D as discussed above. The high percentage of foreign ownership adversely affects the volume of R&D performed in Canada in at least two ways: First, "invisible imports" of technology via multinational corporation substitute for domestically generated innovation. Second, the multinational corporations may retaliate against certain Canadian policy measures (e.g. compulsory licensing) by reducing the share of their global R&D performed in Canada. Recent econometric evidence provides some support for the validity of this hypothesis, at least as far as a sample of large U.S. multinational corporations is concerned.

Narrowing of the gap between cost of research inputs in Canada and in the U.S. and recent trends towards strengthening of patent protection in the U.S., Japan and a number of European countries increase the relative disadvantage of Canada as a location. The management of the R&D process within major multinational companies during the past decade has been characterized by a shift away from domination of the decision-making mechanism by research scientists towards greater emphasis on formalized project selection. Whether this shift works to the advantage or disadvantage of subsidiaries of drug companies located in Canada is not entirely clear; it would seem that, on balance, it may be a favourable development.

The level of Canadian financial incentives, especially tax concessions, in support of industrial R&D compares favourable to that of other industrialized countries. Various aspects of the level and effectiveness of government support for R&D have been investigated in a number of industries and countries. The relevant issues include: the problem of supporting R&D in a small country while the benefits are dissipated throughout the world markets many times the size of the domestic economy;

the "incrementality" effect of grants and tax concessions (assurance that the R&D project supported by government would not have been undertaken without such support) and possible differences in responsiveness of domestic versus foreign-owned firms.

An earlier Canadian study of a sample of firms showed different degrees of responsiveness for firms in different industries, with Canadian-owned firms increasing their own spending per dollar of government grant to a somewhat greater extent that foreign-owned firms. A recent study of a larger sample of Canadian firms also found a positive effect of government grants in support of industrial R&D for Canadian-owned firms, but no response for the foreign-owned firms. U.S. studies of the aggregate relationship between government funding and private R&D spending show estimates ranging between 7 and 20 cents of increase in privately-financed R&D expenditures for every one dollar of increase in government-financed R&D.

The implications of these findings for largely foreign-owned industry in a relatively small country are not completely clear cut. On the whole, however, they would seem to indicate that a further increase in direct government support of pharmaceutical industrial R&D is not the most efficient use of public funds. One line of argument is elaborated on in a recent Canadian study of international comparison of government incentives for R&D. It suggests that when technology can be developed in one location and used without compensation in many others, extensive support of R&D by taxpayers of a small country may not be rational.

Another line of argument is developed in the literature on foreign ownership and transfer of technology via multinational corporation. Its succint summary appears in a comment on the Canadian pharmaceutical industry in an OECD study: "the results of innovation from parent corporations have been so readily available and so economically attractive in the short term that the growth of national innovative technological capacity has been severely inhibited".

The strength of the relevant science base in Canada, relative to other countries with which Canada competes as a location for R&D activity of multinational pharmaceutical companies is examined as well. The main rationale is the observed complementary relationship between the R&D activities in industrial laboratories and those at the universities, hospitals and similar institutions. Two kinds of evidence are employed to formulate an assessment of Canada's relative position. First, expert opinions of the Deans of Pharmacy at several Canadian universities are solicited. Second, data on citations of articles in relevant scientific disiplines is collected and the performance of Canada measured over the period 1973-1980.

Qualitative assessment by experts indicates that only a few of the relevant scientific disciplines (e.g. pharmacokinetics) are relatively strong in Canada. As for specific skills, clinical pharmacologists and toxicologists have been in short supply - an observation made in an OECD study about other countries as well. Various sources comment favourably on the standards and reliability of the Canadian clinical testing establishment, suggesting a potential for Canada as a location for the development and testing stages of the drug innovation process. The university - industry cooperation in Canada is judged as underdeveloped in relation to other industrialized countries.

A quantitative evaluation of the strength of Canada's science base developed from data on citations of scientific articles over the period 1973-1980 indicates that Canada's share of world's science citations in several of the disciplines considered exceeds its share of world's population, GNP, pharmaceutical R&D spending and other possible yardsticks. The strength of Canada's scientific base is thus one of the few determinants of location of R&D activity with respect to which Canada achieves a high score.

On the whole, however, the various theoretical models of the determinants of foreign investment and behaviour of multinational corporations as well as the preponderance of empirical evidence suggest that the odds for a substantial increase in Canada's share of the industrial pharmaceutical R&D activity are not favourable, given any realistic range of policy options.

FOOTNOTES

1) Beyond "perception", very little solid evidence exists. It is indeed sometimes argued that the batch processes in the production of pharmaceuticals are not subject to economies of scale (Egan et al., 1982, p. 5).

2) The importance of "past profitability", "demonstrated ability" and related criteria is evident from the interview reports summarized by Burstall et al. (1981, p. 134). Such past performance indicators are also frequently mentioned by Canadian subsidiaries of the multinational companies in their descriptions of the process of multinational decision-making on location of R&D activity contained in their briefs to the Commission. It is not clear, however, what time horizon is considered or how these criteria are weighted relative to the other factors.

3) This estimate is from Burstall et al. (1981, p. 106). For 1979, OECD (1984, p. 192) gives the share of R&D executed in Switzerland by Sandoz as 61% of the firm's total; the figure for Ciba-Geigy is 60% and data for Roche is not available.

4) Egan et al. (1982, pp. 73-74) note, however, that the annual surveys of the National Science Foundation put the pharmaceutical industry near the top among the industries listed both in the R&D-to-sales ratio and in the ratio of basic research to total R&D.

5) The next few paragraphs draw upon summary of the literature presented in Palda and Pazderka (1982, pp. 14-15).

6) The U.S. Pharmaceutical Manufacturers Association submitted this set of rather detailed figures to a U.S. Senate Committee discussing the Burke-Hartke Bill. The thrust of the submission clearly is an attempt to prove that the U.S. owned multinational pharmaceutical companies basically conform to the intent of the Bill: To reduce the incentives to invest overseas and thus "export jobs" and increase the acceptance of domestically produced goods over foreign imports.

7) The next three paragraphs draw upon the Financial Times, June 7, 1984.

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APPENDIX

Source: CHI Research/NSF Science Literature Indicators Data-Bank (held at the Science Policy Research Unit, University of Sussex, Brighton, England.

NATIONAL PUBLICATION COUNTS

CLINICAL MEDICINE
PHARMACOLOGY

	1973	1974	1975	1976	1977	1978	1979	1980
Canada	184	198	178	250	232	258	288	287
France	232	293	238	275	239	305	317	427
W. Germany	590	591	473	582	571	602	500	530
Italy	135	159	168	179	179	230	259	272
Japan	241	322	277	400	426	467	502	564
Switzerland	94	119	101	124	90	106	109	82
United Kingdom	480	760	547	608	569	618	649	618
USA	2246	2267	2171	2508	2387	2535	2719	2670
Rest of World	1574	1571	1631	1771	1826	1760	1875	1843
World Total	5826	6460	5784	6697	6519	6881	7218	7293

PHARMACY

	1973	1974	1975	1976	1977	1978	1979	1980
Canada	48	52	47	43	45	75	53	43
France	159	91	71	91	60	120	117	152
W. Germany	140	181	174	164	151	172	165	176
Italy	144	169	158	152	164	174	150	116
Japan	801	730	752	784	784	901	746	777
Switzerland	41	19	47	23	13	34	31	25
United Kingdom	50	31	54	53	60	35	39	33
USA	1040	893	953	974	1086	938	1018	911
Rest of World	752	765	758	1065	1027	1089	933	931
World Total	3175	2931	3014	3349	3390	3538	3252	3164

NATIONAL PUBLICATION COUNTS

TOTAL FIELD
CLINICAL MEDICINE

	1973	1974	1975	1976	1977	1978	1979	1980
Canada	2541	2488	2510	2723	2832	2868	2973	2874
France	4365	4066	4203	4192	4585	4175	4361	4482
W. Germany	5246	5557	5195	5100	4997	5517	4799	4938
Italy	1119	1117	1270	1305	1382	1468	1558	1615
Japan	2647	2829	2981	3278	3300	3796	3768	4065
Switzerland	1564	1553	1457	1650	1560	1564	1363	1455
United Kingdom	7906	7871	7622	7726	7509	7722	7368	7459
USA	32638	31691	31334	32920	33516	34966	33975	34612
Rest of World	13183	17337	16908	17705	17916	19133	18662	19033
World Total	76209	74509	73485	76599	77597	81209	78827	80533

BIOMEDICAL RESEARCH

	1973	1974	1975	1976	1977	1978	1979	1980
Canada	1878	1784	1806	1788	1778	1859	1886	1772
France	2875	2848	2937	2682	2712	2440	2511	2664
W. Germany	2393	2574	2356	2620	2373	2682	2643	2667
Italy	1004	1004	1072	1009	673	682	730	726
Japan	1632	1718	1781	2016	2195	2312	2318	2618
Switzerland	412	477	450	510	517	534	578	524
United Kingdom	3857	3979	3972	3863	3842	3769	3674	3731
USA	16115	15607	15901	16271	16197	16611	17649	17582
Rest of World	10989	10641	10969	11132	11101	12079	11642	11983
World Total	41155	40632	41244	41891	41388	42968	43631	44267

NATIONAL PUBLICATION COUNTS

TOTAL FIELD
BIOLOGY

	1973	1974	1975	1976	1977	1978	1979	1980
Canada	1933	1878	1891	2003	2043	1908	2015	1884
France	928	981	946	874	934	895	975	772
W. Germany	946	804	875	931	995	884	1037	950
Italy	111	157	153	138	137	154	169	174
Japan	1284	1158	1244	1312	1346	1469	1472	1486
Switzerland	78	81	58	84	103	94	109	89
United Kingdom	2284	2226	2495	2504	2437	2498	2539	2331
USA	11150	10700	10400	10573	9904	9663	10553	9594
Rest of World	5333	5429	5198	5486	5858	5611	5865	5558
World Total	24047	23414	23260	23905	23757	23176	24734	22838

CHEMISTRY

	1973	1974	1975	1976	1977	1978	1979	1980
Canada	1728	1657	1442	1544	1505	1439	1482	1455
France	3027	3068	2992	2885	2539	2555	2442	2438
W. Germany	2757	2962	2812	2866	2740	3403	2911	3065
Italy	1024	1250	1198	1193	1101	1106	1206	1266
Japan	4226	3957	3745	4072	4060	4208	4708	4833
Switzerland	537	614	565	669	557	562	555	552
United Kingdom	3507	3495	3526	3515	2996	3065	3044	3008
USA	10474	9867	9222	9337	8852	9266	9182	9250
Rest of World	17724	17659	17000	16692	16384	18246	17743	18581
World Total	45004	44529	42502	42773	40734	43850	43273	44448

NATIONAL PUBLICATION COUNTS

ALL FIELDS COMBINED

	1973	1974	1975	1976	1977	1978	1979	1980
Canada	8312	8057	7874	8351	8435	8407	8697	8315
France	11586	11347	11392	10999	11069	10490	10723	10935
W. Germany	12072	12669	11885	12263	11827	13260	12055	12326
Italy	3587	3856	4019	3976	3636	3814	4072	4169
Japan	10831	10714	10780	11862	12111	13153	13514	14343
Switzerland	2726	2863	2678	3060	2840	2894	2745	2727
United Kingdom	18064	18362	18216	18269	17413	17707	17313	17180
USA	73663	71025	69981	72583	71942	73979	75096	74619
Rest of World	54555	53582	52464	53851	54112	57913	56720	57929
World Total	195416	192475	189289	195214	193385	201622	200935	202543